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REMNANTS OF THE VITELLO-INTESTINAL DUCT

A CLINICAL ANALYSIS OF 88 CASES

BY

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(RECEIVED FOR PUBLICATION JULY 1, 1952)

Remnants of the vitello-intestinal duct are said to be present in 2 to 4% of all routine post-mortem examinations, but presumably many people live their allotted span of life despite their presence and at no time have symptoms referable to them. On the other hand, these vestigial structures may make their presence known dramatically in the first few years of life, or, more rarely, in adult life. The complications to which they are subject are serious and are commonest in infants and young children of the male sex.

This paper is based on 88 patients under the age of 12 years who were operated upon in the Royal Hospital for Sick Children, Glasgow, during the past 20 years. In 73 cases there was a definite lesion involving vitelline duct remnants and in 15 the structures were discovered incidentally during laparotomy for some other condition.

Embryology

In the early weeks of foetal life the apex of the mid-gut loop has a wide communication with the yolk-sac, the vitello-intestinal duct. This structure, with its accompanying vitelline artery and veins, gradually becomes reduced in size until complete obliteration occurs at about the seventh week. The obliterative process begins at the umbilical end of the duct and extends towards the intestine and thus it is that the intestinal end persists most frequently in the form of a Meckel's diverticulum. This finger-shaped sac projects from the ante-mesenteric border of the ileum within 36 in. (76 cm.) of the ileo-caecal valve. It generally has a small mesentery in which run the patent remains of the vitelline artery and veins and its distal end is frequently free in the peritoneal cavity. In some instances, however, the diverticulum terminates in a thin cord which may remain attached to the umbilicus or acquire a new attachment elsewhere. This cord is the partially obliterated remnant of the vitelline duct and/or its vessels. More rarely the umbilical portion of the duct remains, giving rise to one type of umbilical polyp (entero-teratoma) which may or may not be associated with an underlying diverticulum. Still more uncommon is the formation of an omphalo-mesenteric cyst (entero-cystocoele) in the partially obliterated duct. In some few instances the whole length of the duct remains patent.

Occasionally an uncomplicated diverticulum is found apparently within the leaves of the ileal mesentery. This anomaly was explained by Moll (1926) who suggested that the diverticulum, having been rotated through 180° by traction of the slowly obliterating vitelline vessels, was pulled against the mesentery and later acquired a filmy covering from it. Various writers have described as 'Meckel's' or 'giant' diverticula structures with a lumen communicating with that of the ileum but truly within the ileal mesentery as proved by their being crossed by the mesenteric vessels. Such structures are more rationally regarded as bowel duplications.

Although the vitelline duct is embryologically related to the ileum, its remnants, where a lumen exists, are not necessarily lined throughout with ileal mucous membrane, and heterotopic tissue is said to be found in 25% of cases (Matt and Timpone, 1940). Ladd and Gross (1941) in their series of 73 cases found ileal mucosa, combined with gastric mucosa in 40, with duodenal in four, with colonic in four and with pancreatic cells in one. In the present series the findings were: ileal mucosa alone, 33 cases; ileal combined with gastric mucosa, 15; and ileal combined with duodenal mucosa, one. In a number of specimens the mucosa had been too extensively destroyed by inflammatory changes for accurate identification of the microscopic structure to be possible.

Numerous explanations have been put forward to account for the presence of aberrant elements. The most acceptable is that of Greenblatt, Pund and Chaney (1936) who suggest that the endothelial lining of the embryo forms cell groups which function as a primitive digestive system and that, while

normally this system regresses as soon as its function ceases, occasionally 'a vestige of heterotopic tissue remains as a consequence of retarded retrogression of the vitello-intestinal duct'.

Clinical and Pathological Findings

In analysing the 73 cases in which the lesion of the vitelline duct was responsible for the clinical picture there were found to be 47 males and 26 females with an age incidence as follows:

Years ..	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12
Number ..	21	4	4	3	11	4	7	6	4	4	4	1

The whole series of 88 cases has been grouped according to the preoperative diagnosis or operative findings thus:

Simulation of appendicitis (acute or chronic)	28	cases
Intestinal obstruction	18	,,
Intestinal haemorrhage	14	,,
Intussusception	8	,,
Umbilical polyp or fistula	5	,,
Incidental finding at operation	15	,,

Simulation of Appendicitis. In the whole group there were 28 cases and no deaths.

ACUTE. In this group there were 22 cases, the sex distribution was equal, and the ages ranged from 2 years to 11 years with an average of 7½ years. The duration of symptoms varied between six hours and eight days and three children gave a history of similar but milder attacks. The symptoms and signs in 20 instances were indistinguishable from those of acute appendicitis in that the illness began with central abdominal colic and vomiting progressing to pyrexia and constant pain in the lower abdomen or to the right of the mid-line. Two cases only varied from this pattern; in one, pain and tenderness were confined to the upper left abdominal quadrant, and in the other the symptoms and signs were of a wandering character, the only case in the series showing this peculiarity although it is sometimes said to be a common feature diagnostic of the condition.

At operation all these children were found to have acute Meckel's diverticulitis. In 13 instances there was perforation of the diverticulum with peritonitis, which was generalized in six. In the remaining nine there was acute inflammation of the diverticulum only. The high incidence of perforation of the diverticulum (60%) is notable. In 17 cases the diverticulum alone was resected, but in four a resection, including the neighbouring ileum, had to be performed. The inflammation had been set up in one case by the presence of a large fish bone which had perforated the diverticular wall, and in another a gangrenous and twisted omphalo-mesenteric cyst attached by one pole to an uninflamed diverticulum was found; histology showed ileal mucosa lining both diverticulum and cyst.

The fact that there were no deaths in this group is mainly attributable to two factors, namely, the greater average age and the similarity of the symptoms and signs to those of acute appendicitis, a clinical picture so well known that most cases were sent to hospital at a relatively early date. In spite of this, however, perforation and peritonitis were present in 13 instances. Ladd and Gross (1941) state that peritonitis resulting from perforation of an inflamed diverticulum is of a rapidly spreading and often fatal type but this has not been our experience; in seven of the 13 cases a localized abscess only had formed.

In the young child pain, tenderness and rigidity due to an acutely inflamed appendix may be situated anywhere to the right of the midline; it is only in the occasional case in which the signs are to the left of the midline or of a wandering character that one can make even a tentative diagnosis of inflamed Meckel's diverticulum. However, when a diagnosis of acute appendicitis has been made and when at operation the gross appearance of the appendix is not in keeping with the clinical picture, search for a diverticulum should always be carried out.

CHRONIC. In this group of six cases there were three males and three females aged from 5 to 9 years. The average duration of symptoms was six months and these consisted of vague peri-umbilical colic and vomiting attacks of varying duration. Diarrhoea was present during the attacks in two instances. Although in all cases a normal appendix and an uninflamed diverticulum were removed, no patient had a recurrence of the symptoms which, according to Ladd and Gross, are due to an upset in peristalsis caused by the presence of the diverticulum.

Intestinal Obstruction. In this group (18 cases, nine deaths) there were 11 males and seven females with ages varying from 3 days to 11 years, the majority being between 4 and 5 years old. The duration of symptoms varied from six hours to six days and only one case had had a similar but milder attack. All these children were extremely ill and their symptoms and signs were in keeping with a diagnosis of severe intestinal obstruction. Dehydration was marked, especially in the younger children, and in 14 instances abdominal distension with ladder

pattern and visible peristalsis were evident. Only in one patient, in whom the umbilicus was markedly indrawn and fixed, could a tentative diagnosis of intestinal obstruction by a vitelline remnant be made.

The operative findings, the varied attachment of the obstructing cord and the associated mortality are shown in Fig. 1. Two patients died pre-operatively and necropsy revealed a volvulus of the diverticulum and associated ileum in both. Haber (1947) and others state that intestinal obstruction is the most common complication but in the present series it accounts for only 25%. Regarding its seriousness all are agreed. Intestinal obstruction by a vitelline remnant is an extremely lethal condition as is evidenced by the 50% mortality. This high figure can be attributed to several factors. The majority of patients are in the 4-5-year age group when the child is uncooperative, making early diagnosis difficult and delaying admission to hospital. Further, the effects of fluid and salt loss which accompany intestinal obstruction are much more serious in the young child than in the adult. In spite of replacement therapy, the cumulative effect is that the child comes to operation ill-fitted to stand a surgical procedure which by the very nature of the obstructing agent must be a lengthy one involving loss of blood and prolonged anaesthesia.

The fibrous cord from the diverticulum, which was the cause of obstruction in 15 cases, is of the consistency of thin string and consequently early strangulation of the snared loop or loops occurs; for this reason resection of varying lengths of bowel and anastomosis was necessary in four cases. The thinness of the cord and the tightness of the constriction may result in early development of transverse lines of gangrene on each limb of the strangulated loop where it underlies the cord. Such areas were present in three cases and had to be oversewn.

Apart from causing strangulation of loops of bowel the fibrous cord attaching the ileum to the umbilicus also provides an ideal axis around which rotation can take place. Volvulus at any age, whatever its cause, is a lethal condition and the two cases in which it occurred were no exception to the rule. Their symptoms of sudden onset and short duration (six and nine hours respectively) were those of fulminating intestinal obstruction with strangulation, and the rapid collapse and death before operation could be performed were due to severe surgical shock.

Intestinal Haemorrhage. In this group of 14 cases with two deaths (12 male and two female) the ages varied from 7 weeks to 10 years. Ten patients were less than 18 months old and the duration of symptoms of eight of these was from 28 hours to two days; the remaining six patients had had similar previous attacks. In 12 instances bleeding was from a peptic ulcer secondary to the presence of gastric mucosa in the diverticulum, and in two cases, although the diverticulum was the source of the haemorrhage, no ulcer or gastric mucosa could be found on pathological examination.

Peptic ulceration in the diverticulum is due to the secretion of hydrochloric acid and pepsin by a gastric mucosal rest which may vary in size from a complete lining to a mere vestige. Those reported cases of ulcers involving gastric mucosa are of doubtful validity, and it is suggested by Aschner and Karelitz (1930) that the actual ulceration occurs in an island of ileal mucosa within the gastric rest.

According to Cobb (1936) the neck of the diverticulum is the commonest site for the ulcer, thereafter the body, the tip and lastly the immediately neighbouring ileum. Maddock and Coventry (1941) report a case in which the ulcer was in the ileum several inches distal to the diverticular orifice. In the present series six ulcers were in the diverticular body, four in the neck, one at the tip and one in the ileum at the diverticular orifice.

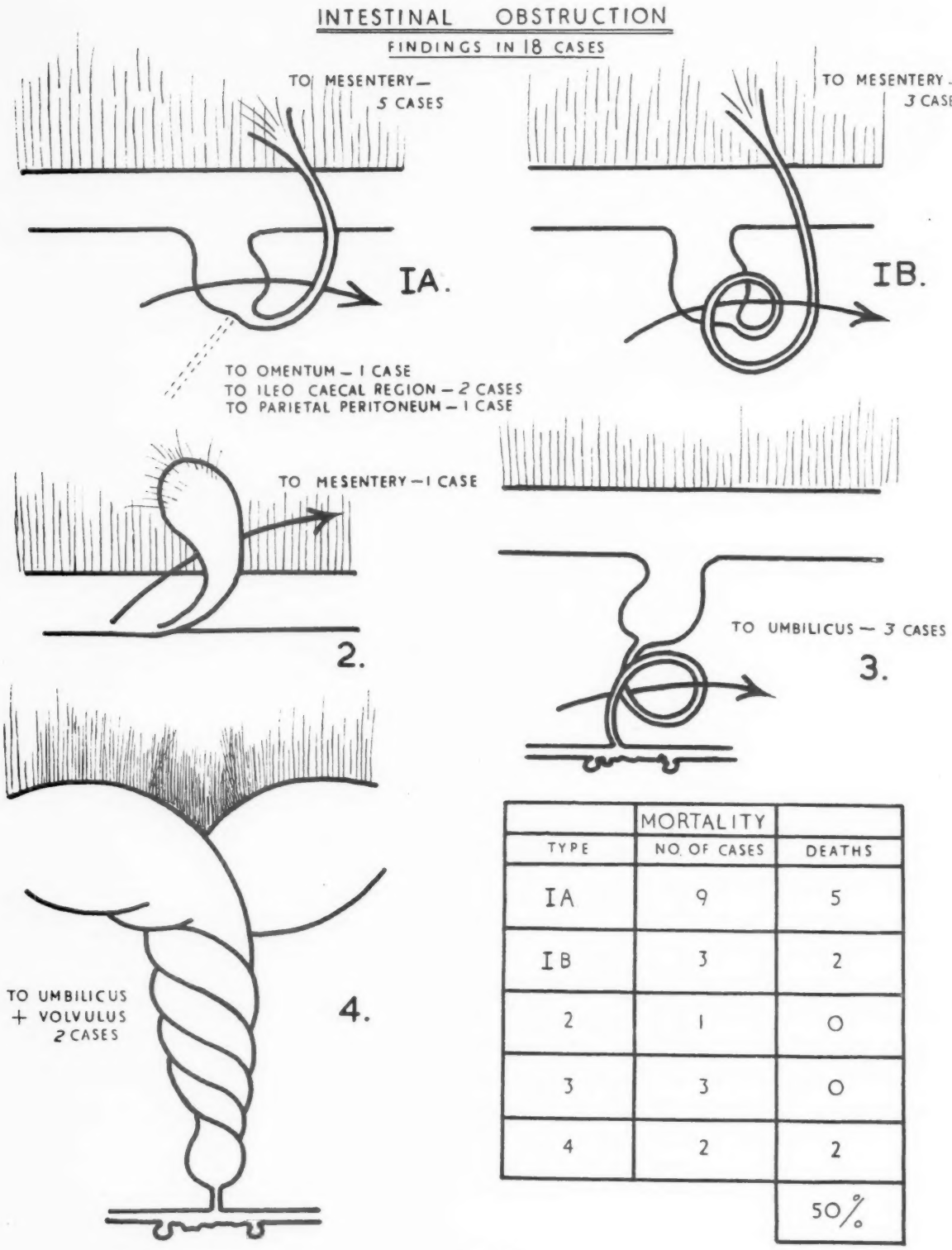
The history of the children in this group was that of attacks of melaena, which, in some cases, had culminated in the passage of unaltered blood, or of one haemorrhage sufficiently alarming to cause the patient to be brought to hospital. Some abdominal pain was usually present but was never severe unless perforation had occurred. Examination of the abdomen was not helpful except in three children under 2 years of age who showed signs of peritonitis and at operation were found to have perforated ulcers. Rectal examination in all 14 revealed the presence of blood, either bright red or altered to a varying extent.

Pre-operative blood transfusion was necessary in eight of the 10 cases below 18 months, their average haemoglobin level being under 50%.

The operative findings and associated mortality were as follows:

No peptic ulcer, diverticulum lined ileal mucosa	2 cases, 0 deaths
Unperforated peptic ulcer, gastric mucosa present	6 cases, 0 deaths
Perforated peptic ulcer plugged by omentum, gastric mucosa present	1 case, 0 deaths
Perforated peptic ulcer and localized peritonitis (abscess), gastric mucosa present ..	2 cases, 2 deaths
Perforated peptic ulcer and generalized peritonitis, gastric mucosa present	1 case, 0 deaths
Peptic ulcer penetrating a neighbouring structure, gastric mucosa present	2 cases, 0 deaths

The last two cases are unusual as penetration of such a peptic ulcer into another structure has not been noted previously in the literature. In one



	MORTALITY	
TYPE	NO. OF CASES	DEATHS
IA	9	5
IB	3	2
2	1	0
3	3	0
4	2	2
		50%

FIG. 1.

instance the ulcer had deeply penetrated the root of the mesentery exposing a large artery and in the other a loop of distal ileum had been penetrated down to the mucosa. In six patients, of whom five were less than 18 months old, a resection of the diverticulum and three inches of ileum on either side, followed by side-to-side anastomosis, was performed and all recovered. The only fatalities were in the two cases with perforation and localized peritonitis.

Because the signs and symptoms vary according to age it is helpful to divide the cases into those under 2 years and those over 2 years. The condition is more common and more severe in the infant, 71% being under 18 months in the present series as compared with 80% under 2 years in that of Ladd and Gross.

Cases Under 2 Years. The passage of a varying amount of only slightly altered blood in a thriving infant in whom there have been no previous symptoms is the cardinal sign. Occasionally the first stool is black or dark but subsequent ones are bright red. Following the passage of the first abnormal stool the signs of haemorrhage—pallor, lethargy and collapse—may rapidly supervene. The 10 infants of this series had passed but little blood before admission and yet presented the picture of internal haemorrhage, the true state of affairs only being revealed on rectal examination when withdrawal of the examining finger resulted in an actual jet of fluid blood and clots projected to some distance. Higgons and Gundy (1937) suggest that this disparity between the clinical condition and the amount of blood known to have been passed is due to the slow entry of blood into the colon and its retention there, the bowel having lost its tone following blood loss. Some degree of spasm of the sphincter must also be present.

The duration of bleeding in the infant is usually short; it was less than 48 hours in eight of the ten cases and in the other two there was a history of bleeding for 24 hours about six weeks previously resulting in admission to hospital from which they were discharged when the haemorrhage stopped. On admission to this hospital both children were found to have perforated ulcers with peritonitis.

Abdominal pain was not a feature in this age group although some parents stated that the infant had had 'wind pains'. There were some slight abdominal distension and possibly some periumbilical tenderness. The three cases with perforated ulcers were recognizable by the features of peritonitis and the finding of blood per rectum.

Cases Over 2 Years. The patients of this group had much longer histories than the preceding ones, the shortest being three weeks and the longest four and a half years; three had previously been in hospital with the same complaint. The principal symptoms, recurring in attacks of varying duration and frequency, were the passage of black stools and occasionally of small amounts of red blood often accompanied by mild abdominal colic. Examination of the abdomen revealed no abnormality. Haemoglobin levels, however, were somewhat low and the faeces contained blood, altered to a varying degree.

That early diagnosis and active treatment are essential in the infant is underlined by three findings in the series. In the first place, in three cases out of 14 (23%) the ulcer had perforated and of these, two patients died despite operation. The high mortality of operation once perforation has occurred is agreed upon by all writers. Secondly, once haemorrhage from the ulcer has begun, a sudden increase may occur at any moment and the haemoglobin level may fall below 50% in a few hours. Thirdly, when the ulcer is of a penetrating nature, as was the case in two patients, a sudden massive and probably fatal haemorrhage from an eroded mesenteric vessel may take place.

The disease in the older child is a much less severe one and its manifestations therefore may recur over a period of years without the child ever becoming acutely ill. Greenwald and Steiner (1931) in their study of 34 cases of different ages came to similar conclusions.

Intussusception. Eight patients (five male and three female) presented with an intussusception. This is 11·2% of the total, slightly less than the percentage of 17 reported by Harkins (1933). None had had a previous attack and the average duration of symptoms before admission was 14 hours. The symptoms were no different from the usually accepted ones, namely spasms of acute abdominal colic and vomiting. In three cases the intussusception mass was palpable only by rectal examination, being situated entirely in the pelvis anterior to the rectum; in several, normal faeces were present in the rectum at first, blood and mucus only appearing some time after the administration of a small enema. At operation, four intussusceptions were of the ileo-ileal type, the remainder, having progressed further, were of the ileo-ileo-colic type. Seven were reducible and had been caused by invagination of the diverticular base; the irreducible one had been started by inversion of a diverticulum lined with oedematous gastric mucosa. Resection was carried out and the infant made an uneventful recovery (Aitken, 1950a).

Intussusception started by a diverticulum is seen more frequently in children and adolescents than in infants. Hertzler and Gibson (1913) in their review of 34 cases record 13 years as the average age, and

Bailey (1938) is of the opinion that it is commonest in adolescence. The average age in this series, however, was only 4½ years, one patient being but 5 months old. The difference in these average figures may in part be due to the upper age limit of admission to this hospital being 13 years.

Umbilical Polyp or Fistula. All patients in this group (five, with one death) were males. In two, aged respectively 2 weeks and 8 months, an umbilical polyp with purulent discharge and excoriation of the skin had been present since separation of the cord. Cautery and ligation had been tried without success. At operation the polyps were found to be connected by a fibrous band to a small Meckel's diverticulum; polyps, bands and diverticula were removed. In both cases the diverticulum was lined with ileal mucosa, but in one the polyp was composed of duodenal and in the other, of gastric mucosa.

Two patients, aged respectively 2 weeks and 4 months, had similar histories and appearances, and on probing the polyp a track running deeply was found. These were visualized by the injection of barium mixture and found to communicate with the small bowel. Polyps and tracks were removed at operation and found to be lined with ileal mucosa.

One child, aged 12 days, had a fistula in the umbilicus through which faeces and flatus were passed dating from separation of the cord. Umbilicus and fistula were removed and found to be lined with ileal mucosa. There was one death (bronchopneumonia) in the group; the others made good recoveries.

In the case of an infant with an umbilical polyp, especially when there is much excoriation of skin or when the usual treatments of cautery or ligation have failed, the possibility of the condition being a vitelline remnant should be considered. Careful probing of many such polyps reveals a small opening in the centre which will accommodate a fine catheter, and, following injection of a barium mixture or lipiodol, a skiagram will confirm its connexion with the small bowel. In many polyps where no fistula exists biopsy and microscopical examination will show the presence of alimentary mucosa, and in such cases exploration of the abdomen is sound practice owing to the probable association of a Meckel's diverticulum and cord. In the type of case with a large umbilical fistula through which faeces is passed the pathology and diagnosis are not likely to be in doubt. Although no case of prolapse of the ileum through such a fistula occurs in the series this complication is not so rare as one might expect. Kirtland (1951), reporting one case, states that of the 131 cases of patent vitello-intestinal duct so far recorded in the literature, prolapse had occurred in 28 instances. He therefore deprecates the practice of 'waiting until the baby is older' to operate on an umbilical fistula, and advises early and prompt operative treatment.

Incidental Finding at Operation. In the hospital in which these patients were treated it has been the practice to search for a Meckel's diverticulum in each case when an abdomen has been opened at operation unless there is a definite contraindication, such as the danger of spreading infection. In 13 cases of this group of 15, with no deaths, an inflamed but not grossly pathological appendix had been found and removed. The diverticulum was found on further search and removed.

In two babies, aged 1 day and 12 hours respectively, operation was performed for cure of an exomphalos, and in both the diverticulum was found firmly adherent to the fundus of the sac. In one, the diverticulum was separated but not otherwise interfered with until it was removed when the child was 8 years old, following attacks of abdominal pain and vomiting. In the second case, one loop of ileum entered the diverticulum, while two loops with separate mesenteries emerged; these continued into a duplicated caecum, colon and rectum (Aitken, 1950b).

Discussion

Complications associated with vitello-intestinal remnants are varied and may be serious, especially in children under 5 years of age. In the 88 cases reported in this paper there were 15 deaths, a mortality rate of 17%. When the non-pathological cases are excluded the mortality is 20·5%. Six of the deaths were in the first year of life, and six in the first to fifth years.

Cases resembling acute appendicitis and those in which the duct was found incidentally, all recovered. The one death in the umbilical polyp group was fortuitous. The most serious complication is intestinal obstruction; of the 18 patients presenting with this condition the majority were in the 4-5-years age group and nine died. On the other hand, intestinal haemorrhage (two deaths in 12 cases) and intussusception (three deaths in eight cases) occurred mainly in the infants and are the next most serious complications. It seems obvious from these figures that early recognition and active treatment of these three types of complication is of the utmost importance.

A number of patients in this series were sent to hospital unduly late. The delay in recognition of the child's serious condition was especially noticeable in the intestinal obstruction group where in several instances the possibility of obstruction was not considered until constipation and abdominal distension

had become marked. It cannot be too strongly emphasized that these are late signs; the two early signs of value in diagnosis are splashing on succussion and increased peristalsis, both of which can easily be elicited by auscultation of the abdomen. If radiography is available the finding of fluid levels in a straight skiagram of the abdomen with the child upright confirms the diagnosis. When these signs are present and when there has been no previous intra-abdominal disease, a vitelline remnant is one of the likeliest causes of intestinal obstruction in the 4-5 years age group.

In the intestinal haemorrhage group especially, not a few children had been discharged from hospital after a few days having had no treatment because bleeding had ceased, the child appeared perfectly well, and investigations, which included blood examination, sigmoidoscopy and barium meal skiagrams, had been consistently negative. With regard to the last, the lack of radiographic evidence of gastro-intestinal abnormality in these cases merely imparts a false sense of security as the possibility of demonstrating a Meckel's diverticulum by this means is remote.

The diagnosis of an ulcerated Meckel's diverticulum should always be considered in the case of a thriving infant who suddenly becomes pale and listless although it may have passed but one melaena stool or a small quantity of blood. Should the haemorrhage cease, as sometimes happens, especially in the older child, the condition should not be lightly dismissed and the patient discharged from hospital but, failing a reasonable explanation of the bleeding, a laparotomy should be performed. There is no place for expectant treatment in the management of these cases if the risk of further and possibly fatal haemorrhage or perforation and peritonitis is to be avoided.

As regards the group presenting with intussusception, the signs in the early case may be misleading. The intussusception, being initially an ileo-ileal one, is at a more proximal level in the bowel than the common ileo-colic type and consequently normal stools may be passed before blood and mucus appear in the rectum. Moreover, the intussusception mass being mobile at first may gravitate into the pelvis and lie concealed therein. Time may be saved in such doubtful cases by the administration of a small enema and by careful rectal examination with the intent not only of obtaining blood and mucus but also of examining the pelvic contents.

Summary and Conclusions

A series of 88 children, in whom remnants of the vitello-intestinal duct were present, is analysed. The cases are discussed under six headings according to the pre-operative diagnosis and operative findings.

The overall mortality of the pathological cases in the series was 20·5%. The mortality is greatest at ages below 5 years and especially in the first year of life.

Of all the complications, acute diverticulitis simulating acute appendicitis was found to be the commonest, and intestinal obstruction to have the highest mortality.

Intestinal haemorrhage due to peptic ulceration was seen most frequently in the first 18 months of life, intussusception and intestinal obstruction between 4 and 5 years, and acute diverticulitis between 7 and 8 years.

Intestinal haemorrhage and intestinal obstruction cases, on the whole, were diagnosed and admitted to hospital late. Reasons and remedies for this have been suggested and the importance of early recognition and active treatment of these two complications have been stressed.

I wish to thank Mr. A. P. Laird, in whose wards many of these cases were treated, for his constant help and encouragement. I am indebted to Mr. Matthew White for his permission to include cases treated in his wards, and to Professor Stanley Graham for his valuable assistance in the preparation of this paper. The cooperation of the Pathology Department is much appreciated.

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OVARIAN AGENESIS OR THE PTERYGIUM SYNDROME

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 11, 1952)

Ovarian agenesis and the pterygium syndrome are terms recently coined. They represent two rare conditions infrequently reported in the literature. For an extensive survey of the historical development of these clinical pictures the reader is referred to papers by Wilkins and Fleischmann (1944b), Rossi and Caflisch (1951), Reiniger (1951) and Granrud (1952).

A short review reveals that Funke in 1902 gave the first account of deficient sexual development combined with pterygium colli (webbed neck). In 1938 Turner described the triad of infantilism, pterygium colli and cubitus valgus. In 1942 Varney, Kenyon and Koch and Albright, Smith and Fraser showed by means of hormone analysis of urine that similar cases of deficient sexual development were due to primary deficiency of the ovaries. Lastly Wilkins and Fleischmann (1944b) introduced the term 'ovarian agenesis' based on findings at biopsy and necropsy. At the site of the ovaries were small, white ridges lacking germinal epithelium. In a few cases of this so-called sexual infantilism the ovaries have reached a later stage of foetal development, but never the stage of a normal newborn infant's ovaries.

Wilkins (1950) connects the following clinical features with ovarian agenesis: infantile breasts, labia, clitoris, vagina and uterus, as well as rudimentary or missing ovaries. Sexual hair is usually present, though in a moderate degree and often not till the age of 14 to 16 years. Growth in height is nearly always stunted, yet a case with normal height has been described. The maturation of the bones is approximately normal, as also is the development of the teeth. There is increased gonadotropin excretion in the urine but only after the age of 12 years, as urinary excretion of gonadotropin is very small before puberty. The excretion of 17-ketosteroids is normal or slightly reduced. To this picture may be added a series of conditions of varying frequency: pterygium colli, the Klippel-Feil syndrome, a lowered hairline of the neck, hypoplastic mandible, ocular abnormalities, deafness, coarctation of the aorta, hypertension, cubitus valgus, scoliosis and slight osteoporosis. The I.Q. is usually normal. Wilkins maintains that it is not known whether males present any condition corresponding to ovarian agenesis. In this connexion it may be noted that some cases of Turner's syndrome in the male have been recorded by Dorff, Appelman and Liveson (1948), Cunningham and Harley (1951) and Rossi and Caflisch (1951) among others. As to the incidence of the different symptoms, Wilkins and Fleischmann (1944b) point out that among 32 cases of ovarian agenesis 13 were associated with pterygium colli.

In short, ovarian agenesis is characterized by deficient sexual development combined with a varying series of anomalies. Most of the symptoms can be regarded as developmental defects and malformations. The aetiology is unknown. According to van Creveld and de Vaal (1949) ovarian agenesis has not been observed as a hereditary disease. On the other hand Kaijser (1949) has reported six cases in three of which the patients were closely related to each other, and Granrud (1952) reports a case of Turner's syndrome with familial traits of the disease.

Rossi (1945) introduced the pterygium syndrome, and in 1951 Rossi and Caflisch analysed it on the basis of 177 cases collected from the literature as well as 20 of their own cases. Their analysis comprised such conditions as the status Bonnevie-Ullrich, in addition to pterygium specially characterized by lymphangiectatic oedema, muscle aplasia, disturbance of the cranial nerves, retardation of growth, skeletal anomalies, etc.; Turner's syndrome; Nielsen's dystrophia brevicollis congenita, particularly recognized by the Klippel-Feil syndrome, pterygium colli and anomalies of the hairline of the neck; and lastly pterygo-arthromyodysplasia congenita: pterygium of the limbs, muscle aplasias and defects of the joints, arthrogryposis. Pterygium was found in all 197 cases, the neck being involved in 135 of them. Sixty-eight cases showed infantilism of the Turner type, among which 12 were distinct, and there were three mild cases in the male. Of the 197 cases, the sex was known of 115 females and 67 males, and was not stated in 15 cases. Other manifestations of the syndrome found in varying

degree were stunted growth, anomalies of the spine, cubitus valgus, hypoplastic mandible, a characteristic physiognomy described as *bec de lièvre* or *greule de loup* (hare beak or wolf jaw), congenital heart defects (usually coarctation of the aorta or defective interventricular septum), malformations of the hands and feet, lymphangiectatic oedema, muscle aplasias, and disturbances of the cranial nerves or possibly of the muscles supplied by them.

It will be seen that most of these features are the same as those connected with ovarian agenesis. We note particularly that in one-third of the cases there were signs of infantilism and hypogonadism. It seems that the occurrence of pterygium to a certain extent is familial. In 27 cases Rossi and Caflisch found hereditary traits. The same authors collected 120 cases of primary hypogenesis or agenesis of the gonads from the literature, pterygium being present in half of them.

It may well be asked whether ovarian agenesis and the pterygium syndrome represent two different conditions. Primary hypogonadism is probably a more proper term than ovarian agenesis, because complete agenesis of the ovaries is not always present, and because Turner's syndrome is reported in the male. From one-third to a half of the recorded cases of primary hypogonadism present pterygium. Fully one-third of the recorded cases of the pterygium syndrome show primary hypogonadism. Is such a frequent coincidence of two such rare conditions merely accidental? One should rather assume that they represent two different manifestations of the same syndrome of defective development and malformations. In both ovarian agenesis and the pterygium syndrome the aetiological factor has evidently operated at the organo-genetic stage of development. The injurious factor or factors will not always cause clinically uniform results, as both the mentioned syndromes include a series of variable features. There should be no reason to stress the pterygium syndrome as a more essential symptom than the hypogonadism or vice versa. A more comprehensive term is needed.

The aetiology and pathogenesis of this condition are unknown. Both the pterygium syndrome and ovarian agenesis may appear hereditary. Ullrich (1938) has tried to find conformity between pterygium colli and the myelencephalic blebs of the neck of Bagg-Little mice raised by inbreeding mice exposed to x-rays and showing a series of malformations. According to Bonnevie (see Reiniger, 1951), these blebs are formed early in foetal life owing to increased pressure of the liquor. They extend to the periphery, the damage done by them depending on their physical action. Similar blebs in the human foetus have been described (Reiniger, 1951), but it is difficult to apply Bonnevie's theory to more than a few of all the manifestations of this syndrome (Glanzmann, 1951; Launay, Matet and Colbert, 1951).

Treatment

The most important feature of the syndrome requiring treatment is the deficient sexual development. Here substitution therapy with gonad hormones is rational. According to Wilkins (1950) females should be given oestrogenic substance, usually stilboestrol, in doses from 0·5 to 5 mg. daily, usually 1 mg., for several months. When the genitals have reached the stage of adolescent development, or endometrial bleeding occurs, cyclic treatment is instituted. For two weeks stilboestrol alone is given, then for one week stilboestrol plus progesterone, 10-30 mg. daily, in order to simulate normal cycles, with no drugs during the fourth and last week of the cycle. Bleeding usually occurs two to three days after treatment is stopped. This treatment must be permanent. Of course fertility cannot be achieved.

A case has been recorded where this treatment was supplemented by testosterone on the assumption that if the suprarenal cortex is partially defective, shown by the absence of sexual hair and reduced excretion of 17-ketosteroids, the provision of androgen may be indicated. The assumption was justified by the development of sexual hair and increased growth in height, a result not achieved by stilboestrol treatment (van Creveld and de Vaal, 1949).

Among the other manifestations of the syndrome, pterygium colli may be treated by cosmetic operation. The hypertension requires a protective regime.

The expectation of life of these patients has not been calculated statistically. It may be impaired by hypertension or heart disease.

These reflections are due to a characteristic case of the pterygium syndrome, or ovarian agenesis if that term seems more convenient, treated at the Paediatric Clinic, Bergen.

Case Report

A girl, H.D. (1090/51), was barely 16 years old when first seen on June 28, 1951. Her paternal grandmother was of small stature, as were several of her father's siblings, without other striking external characteristics; no cases of malformation in the family were known. Her mother was well during the pregnancy, she had suffered from no infection, and had not been exposed to x-rays. The patient's weight was 4,000 g. and length 50 cm. There was nothing noteworthy about the physical or mental development during infancy and early childhood. She acquired the ordinary children's diseases before she was 7 years old, and had also suffered from

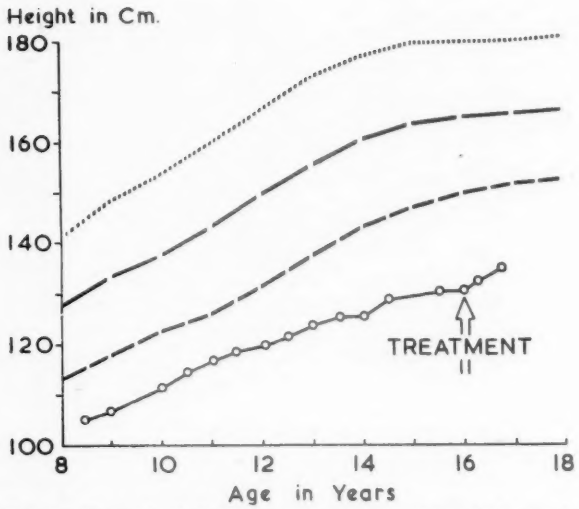

FIG. 1.—The patient's height-curve (o——o——o) in relation to the normal figures (according to Broman, Dahlberg and Lichtenstein, 1941).

pneumonia and otitis media. Otherwise she was in good health. When 10 or 11 years old she developed several small, brown naevi on the face, trunk and limbs. She attended school at the ordinary age, meeting its requirements without difficulty. Her temperament had been normal. When she first went to school it was noticed that she was shorter than her companions of the same age, but it was not until five or six years later, about the age of 13, that she was suspected of suffering from a more serious disturbance. The secondary sexual signs did not develop, the menarche failed. Her height and weight had been measured regularly since her second year in school. Fig. 1 shows her height in relation to the average height for normal girls of her age. On the whole her height kept about 20% below the average. She had not suffered from headache, visual disturbances, dyspnoea or oedema, and had received no treatment before admission to the clinic.

On admission she was found to be of short and stocky build, well proportioned. Her height was 130 cm. (average for her age 164·5 cm.); her weight was 37·5 kg. (average for her height 27·5 kg.). Her face was peculiar (Fig. 2) as she had slight internal epicanthus, a short and stumpy nose, a hypoplastic mandible, and an upper lip so short that it gave the mouth an appearance suggestive of a rodent's. She had 24 teeth, the 12-year molars being missing, and a high palate. Respiration was untroubled. There was no cyanosis. Blood pressure in the arms was about 195/110 mm. Hg, in the legs about 255/210. Subsequent repeated recordings were about 180/115 and 250/170 respectively. On the forehead were dilated veins. There was no oedema. The skin presented several small, brown naevi, but appeared otherwise normal. The hair of the head was dry and thick, with a lowered hairline on the neck. The neck was short, with bilateral pterygium colli of moderate degree. The ears appeared normal. The circumference of the head was 55 cm. The thyroid gland was not enlarged. The thorax was arched and well developed. The breasts were infantile. The second cardiac sound over the base of the heart was accentuated, but a physical examination of the heart proved negative otherwise. The lungs and abdomen showed no abnormality. The external genitals were infantile, and there was no sexual hair. The limbs were normal except for a moderate degree of cubitus valgus. No neurological abnormalities were perceived and mentally the girl was normal. Digital exploration per rectum by a gynaecologist revealed a small uterus, and no ovaries could be palpated. Examination by an ophthalmologist showed rather ill-defined nasal borders of the optic discs. At the centre of the fundus oculi the vessels were tortuous, and the veins to some extent dilated. There was no arteriovenous compression, no oedema of the retina, haemorrhages, or signs of degeneration.

Electrocardiographic examination showed left axis deviation. Radiologically the heart showed an enlarged left ventricle and a rather wide aortic arch.

Findings on intravenous urography were normal.

X-ray examination of the bones revealed centres of ossification and epiphyseal lines within normal variations. The sella turcica was normal. The impressiones digitatae were not increased. The intervertebral spaces were somewhat narrowed. Of the lower thoracic vertebrae, the upper and lower surfaces were rather uneven. The lower metaphysis of the right femur showed cystic osteoporosis of the size of an almond.

Laboratory Findings. The ordinary urine tests were

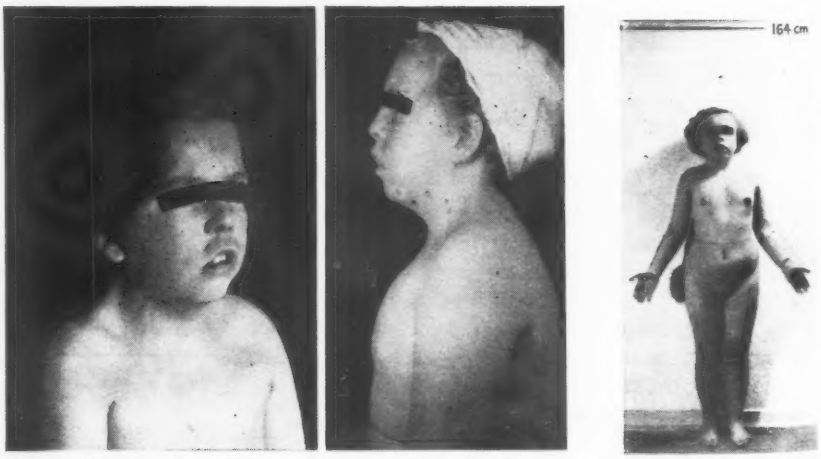

FIG. 2.—Photographs of H.D. when about 16 years old. Note the pterygium colli, the lowered hairline of the neck, the curious physiognomy (*bec de lièvre*), numerous naevi, the stocky build with proportioned stunted growth and cubitus valgus and the absence of sexual hair. (The photograph on the right is taken after onset of treatment, thus pigmented areola.)

negative. Normal figures were also found for dilution and concentration of the urine, diuresis, blood urea level, carbon dioxide concentration in plasma, urea-clearance and creatinin excretion on the tolerance test. The blood picture was normal, as were the figures for serum sodium, potassium, chlorides, calcium, phosphates, alkaline phosphatase and cholesterol. Basal metabolism was normal. The blood sugar curves presented a normal appearance on glucose tolerance and insulin tolerance tests. Tuberculin and Meinicke reactions were negative. Hormone analysis of the urine gave follicle-stimulating hormone*, about 111 m.u./litre; luteinizing hormone, 33 m.u./litre; oestrogens, 17 m.u./litre. The excretion of 17-ketosteroids is recorded in Fig. 3.

Treatment. From August 26, 1951, stilboestrol ('stilbofollin nyco') was given by mouth, 0·5 mg. daily for three days, and later 1 mg. daily. After seven weeks of treatment the first vaginal bleeding occurred, and stilboestrol was withdrawn. The bleeding lasted five or six days, and stilboestrol was given again after one week. Bleeding reappeared when the drug was withdrawn after another five weeks of treatment. Since then bleeding, lasting five to six days, has begun regularly the day after stilboestrol is withdrawn. Since December 11, 1951, cyclic treatment has been given, with stilboestrol for three weeks and no treatment during the fourth week. From March 7, 1952, the dosage was reduced to 0·5 mg. daily, with bleeding occurring as regularly as before the reduction in dosage.

On December 24, 1951, progesterone was added to the treatment, in the forms of anhydroprogesterone lingualettes, ('progestin P', Organon) 10 mg. daily, in the third week of the cycles. This has produced no change in the clinical picture.

A few days after the beginning of treatment with stilboestrol the breasts were slightly tender. After six weeks of treatment the areola showed distinct pigmentation, the breasts were slightly enlarged, and the nipples prominent. Later the mammae enlarged but little.

During treatment there was no growth of sexual hair. Since March 17, 1952, testosterone propionate has been added ('testin nyco', kindly placed at our disposal by Nyegaard and Co., Oslo), 25 mg. intramuscularly twice weekly for the first three weeks of the cycles. Two months later pubic hair began to grow.

The results of the treatment are shown in Fig. 3, with the height and weight measurements and the 17-ketosteroid excretion. The height shows improvement during treatment (cf. Fig. 1). The 17-ketosteroid excretion has kept distinctly below normal values, and, most noteworthy, has fallen to zero after treatment with testosterone.

The blood pressure has remained unchanged during treatment. The centres of ossification and epiphyseal lines have developed normally as judged by x-ray controls. The patient has complained of no discomfort during treatment.

This case presents typical features of the pterygium syndrome as well as ovarian agenesis. An exploratory laparotomy might be desirable, but is not necessary to confirm the diagnosis. It may be of interest to deal with the following points in some detail.

With regard to the sex characteristics, it is held that the development of the breasts, labia minora, vagina and uterus is stimulated by oestrogen, the mammary glands by progesterone, the labia majora and clitoris by androgen, whereas the growth of sexual hair is chiefly regulated by androgen, possibly by an interplay of oestrogen and androgen (Wilkins, 1950). Engstrom and Munson (1951) maintain that the factors influencing the growth of sexual hair are complex and not fully understood. In ovarian agenesis there is sometimes reduced excretion of 17-ketosteroids, as well as absence of sexual hair. This

* Follicle-stimulating and luteinizing hormones and oestrogen were determined at Nyegaard & Co.'s biological laboratory, Oslo. Normal figures for follicle-stimulating hormone are about 33 m.u./l. For a short time during puberty the excretion may be increased to between 33 m.u./l and 110 m.u./l. Luteinizing hormone is not excreted in the urine under normal conditions. Oestrogen in childhood, during the climacteric in women and in men is below 17 m.u./l. In normally menstruating women it is from 17 m.u./l to 167 m.u./l determined by the Allen-Doisy method. 17-Ketosteroids were determined by K.Fr. Støa, of the biochemical laboratory, Haukeland Hospital, Bergen, by Hamburger's method. The normal values for a girl of our patient's age range from 2·4 to 14·2 mg./24 hours, with 8·6 mg./24 hr. as the mean.

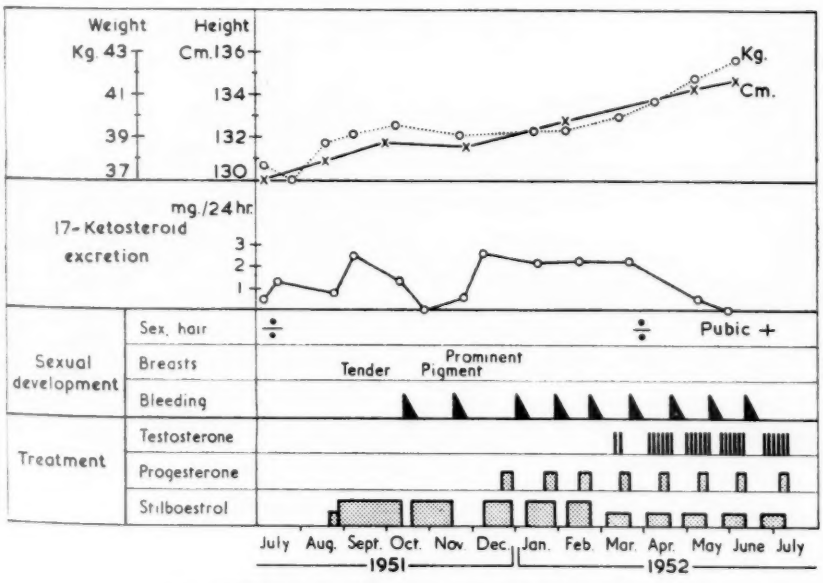

FIG. 3.—The results of hormonal treatment of the patient.

may indicate a reduced production of androgen. Finding no failure of the electrolyte balance or glucose metabolism, we are possibly dealing with a partial failure of the adrenal cortex. A case of ovarian agenesis has been recorded in which post-mortem examination revealed a hypoplastic adrenal cortex (Atria, Saur and Donoso, 1948), and in which sexual hair was absent. Thus androgen therapy in ovarian agenesis should be rational.

In our case the excretion of 17-ketosteroids was reduced during treatment with testosterone. This may have been accidental, or testosterone may have suppressed the androgen function of the adrenals directly or via the hypophysis. At any rate it is noteworthy that a weekly supply of 50 mg. testosterone intramuscularly was followed by a reduction of the 17-ketosteroid excretion to 0 mg./24 hours.

Why is growth in height stunted in ovarian agenesis? It is unlikely to depend on hypofunction of the hypophysis or the thyroid gland. Inhibition of growth due to some other known cause (cerebral, cardiac, renal, etc.) may also be dismissed. Ovarian deficiency has been discussed as a possible cause. With increased oestrogen production, as in granulosa cell tumour, growth in height may be increased (Warkany, 1950). On the other hand castration before puberty may lead to increased growth. This excludes the agenetic ovaries as the origin of the stunted growth. It is found that androgens may stimulate growth, particularly during the years of puberty. As already pointed out, ovarian agenesis is often associated with signs of reduced androgen production. If this reduction should be responsible for the diminished growth, the stunting is unlikely to appear before puberty. It is not so. At the age of 8 years our patient was 20% below average in height. It is commonly supposed that this inhibition of growth depends on genetic factors, being a developmental anomaly in line with other manifestations of the syndrome (Wilkins, 1950).

Several authors apply the term 'sexual infantilism' to the clinical picture presented by ovarian agenesis (Wilkins and Fleischmann, 1944a; van Creveld and de Vaal, 1949; Kaijser, 1949; Wilkins, 1950; Granrud, 1952). It has not been possible to find any definition of this term. Infantilism generally indicates an inhibition of the whole organism in an infantile phase and may be due to deficiency of a special organic system, infantilism being further classified according to its cerebral, cardiac, renal or other origin respectively. By analogy sexual infantilism should imply stunted growth due to hypofunction of the gonads. From what has already been said it is evident that the term sexual infantilism does not cover the conditions, as far as they are known, and should not be applied. Gonad hypofunction can hardly be responsible for more than the sexual underdevelopment.

Hypertension is no rare finding in ovarian agenesis. Among 15 cases hypertension was found in 10 (Wilkins and Fleischmann, 1944b). In these cases the upper limit of the systolic pressure was about 150 mm. Hg, with a diastolic pressure about 110 mm. In our case the blood pressure was remarkably high. It has not been possible to discover definite aetiological factors accounting for hypertension, cases with coarctation of the aorta excluded. No renal or adrenal cause has been demonstrated.

In ovarian agenesis fairly extensive osteoporosis is usually found. The cystic form presented by our case has also been reported before (Wilkins and Fleischmann, 1944b). The development of the teeth is said to proceed normally. In our case it was somewhat delayed.

We do not know to what extent, if any, there is a connexion between the multiple naevi observed in our case and this syndrome of developmental defects. Haney (1952) has lately reported a case of ovarian agenesis with numerous moles on the skin.

When primary hypogonadism takes the monosymptomatic form with only deficient sexual development its recognition before puberty may be very difficult, and the diagnosis will apparently not be supported by hormone analysis. However, a case has recently been reported in which increased gonadotropin excretion was observed in a girl barely 3 years old suffering from ovarian agenesis (Silver, 1951).

Summary

The history and symptomatology of ovarian agenesis and the pterygium syndrome are surveyed. Their aetiology and pathogenesis are discussed. In view of the features which these two syndromes have plainly in common, it is argued that they should be regarded as different manifestations of the same syndrome.

Treatment and prognosis are reviewed.

A report is given of a typical case, treated with stilboestrol, progesterone and testosterone. Some of its symptoms are discussed. The term 'sexual infantilism' is criticized.

I should like to thank Professor Alfred Sundal for his help and encouragement in preparing this paper.

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CHONDRODYSTROPHY WITH ECTODERMAL DEFECTS

BY

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The following case report is that of a child in whom chondrodystrophy is combined with defects in ectodermal development and who is therefore reminiscent of cases described in 1940 by Ellis and van Creveld. There are, however, interesting differences which cast doubt upon the identity of the syndromes.

Case Report

M.H., the elder of two girls, first came under observation by one of us (E.J.G.) in 1943 because of multiple orthopaedic deformities. Since then she has received both orthopaedic and plastic surgical treatment which have improved her in some measure both in function and appearance. The following description records her condition in 1950 when aged 12.

Delivery was normal at term. Her mother suffered during pregnancy from hyperemesis, and there is said to have been oligamnios. Birth weight was 7½ lb. The child progressed well, and, apart from an unexplained short illness at 9 months, her health was good throughout childhood. She talked and walked at the average times, and teeth started to erupt at 8 months. Orthopaedic treatment was begun at the age of 4, and treatment was carried out at a plastic unit when aged 9.

M.H. is the child of young unrelated parents with no relevant history on either side. The younger child (a girl aged 4 in 1950) is normal.

The patient is an intelligent and cheerful child of average height and nutrition. There is an exaggeration of the normal spinal curvature when she stands, and there is gross knock-knee (Fig. 2). Because of stiff joints and deformity of the feet her gait is slow and awkward.

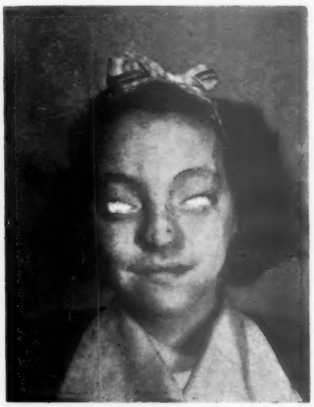

FIG. 1.

Measurements are as follows: Height, 4 ft. 5 in.; weight, 69 lb.; head circumference, 20 in.; symphysis to sternal angle, 13¾ in.; chest circumference, 31-32½ in.; interpupillary distance, 2·6 in.; symphysis to vertex, 24¾ in.; symphysis to sole, 28¾ in.; limbs (upper), 17 in., (lower right, 30¾ in., lower left), 29¼ in.

FIG. 2.

The skin is generally sallow. There are many areas of brown pigmentation, especially on the face. In pigmented areas, some of which measure several inches in their longer dimension, the skin is puckered and depressed beneath the surface of the surrounding normal skin. At the right outer canthus one such area is responsible for ectropion of the upper lid. One or two of the larger patches have previously been excised. The skin of the nose is pitted by numerous very small depressed patches of this kind. Areas of abnormal skin are largely confined to the face, hands and feet, but one or two puckered areas are to be found on the thighs also.

The mucous membranes are normal, with the exception of the mucosal surface of the lower lip. Here a gingivolabial sulcus has been fashioned by plastic surgery. Before that the mucous membrane is said to have passed directly from the lower lip to gum without the normal sulcus.

The eyes are widely separated and rather proptotic. The palpebral fissures are oblique, slanting upwards and outwards (Fig. 1).

The nose has large, widely separated nostrils. The ears are normal.

The hair is dark brown and abundant on the scalp, but axillary and pubic hair is scanty.

Only 23 teeth have erupted. They are very irregular in spacing and in lateral alignment. Only one upper incisor is present on each side and three premolars are unerupted. There is a high vault to the hard palate, with the two sides meeting at an obtuse angle in the midline.

The chest is barrel-shaped with, however, good expansion. There is kyphosis of the mid-thoracic region with some scoliosis convex to the left. The spine is flexible.

As far as the wrist the contour of both upper limbs is normal. There is severe valgus deformity at the right knee. The left leg is 1½ in. shorter than its fellow, and the thigh and leg circumferences on this side are 1 to 2 in. less. Also there is valgus deformity at the knee and some bowing of the leg, so that the inner border is concave.

There is some limitation of flexion of the right elbow, while extension, pronation and supination of the left elbow are greatly restricted. Left wrist movement is in all directions much reduced. Metacarpo-phalangeal movements are reduced in both hands, while inter-phalangeal movements are almost completely absent. There are 10 degrees of hyperextension at the right knee with an equivalent loss of full flexion. Otherwise knee movements are full, but the patella is displaced to the outer side of the left knee joint. There is restriction of movement at the left ankle and at the metatarso-phalangeal joints on both sides. The interphalangeal joints of toes 2 to 5 on the right side, and of the first and second toes on the left side, are fixed. In the remainder movement is limited.

The hands and feet are greatly deformed (Figs. 3 and 4). Some fingers are flattened in the dorso-ventral plane, and finger length is disordered. Thus the index finger is the shortest in both hands, and the fifth digit the longest. Minor joint deformities, such as acute forward flexion of the terminal phalanx of the right fifth digit, are present besides the limitation in movement already described. Interdigital webbing (up to the distal end of the first phalanx) is present between several fingers, and plastic operations have removed it from others. The left hand has a side-to-side curvature apparently due to puckering and contraction of the skin of the palm. There are also areas of thin, red, shiny, telangiectatic skin over the distal phalanges. The finger nails are dystrophic; that of the fourth right finger is thickened and ridged while those of the thumb and index are flat. The third left finger nail surmounts the end of the finger, with its surface facing distally, and the fourth left nail is also ridged and thickened.

The big toes show considerable valgus deviation and over-ride the neighbouring toes, which are irregular in length, possess interdigital webs, and are closely bunched together. The skin shows numerous callosities, and over the soles is puckered and contracted. Over the lateral aspect of the foot on each side there is a band of telangiectatic skin. The toenails are normal in shape and texture.

There are no abnormal signs in the central nervous or respiratory systems, and the abdomen is normal to palpation. The urine contains no abnormal ingredient.

The heart is not clinically enlarged but a soft diastolic murmur is to be heard at the left border of the sternum at its lower end. The significance of this is uncertain and there was unfortunately no opportunity to amplify this finding. Blood pressure was 135/85 mm. Hg.

X-ray Examinations. These were performed in 1943, 1947 and 1950, when the child was 6, 10 and 12 years old respectively.

No convincing enlargement of the heart shadow was seen.

Findings in the bones of hands and feet are very grossly abnormal and pathognomonic of the Ellis-van Creveld syndrome (Figs. 5 and 6). There is a general bone dysplasia resulting in bizarre shapes of most bones. During the years a tendency towards increasing synostoses is evident. The bone age as seen in carpal and tarsal bones and epiphyses is normal.

RIGHT HAND. In 1950 the second to fifth metacarpals were stunted, broad and barrel-shaped. Ankylosis of the inter-phalangeal joints of the second and third fingers was seen with stunted growth of these fingers. A large horseshoe-shaped bone is formed by the synostosis of the second and third metacarpals at their bases, the multangulum minor and the capitate bone.

LEFT HAND. In 1950 it was grossly stunted. The first and second phalanges of the little finger are developed in pairs, all four being fused into a single, oddly shaped bone. A longish bone formation overlying the ulnar edge of the carpel region and fused with the os pisiform probably represents a supernumerary digit. There is also a fusion of the first and second phalanges of the second finger. The inter-phalangeal joints of the second and fourth fingers are almost ankylosed. Very extensive synostoses are to be seen between the carpal bones and the bases of the metacarpals. There is no distinction between the cortex and spongiosa of several of these bones.

FEET. The second to fifth toes of the right foot are

FIG. 3.

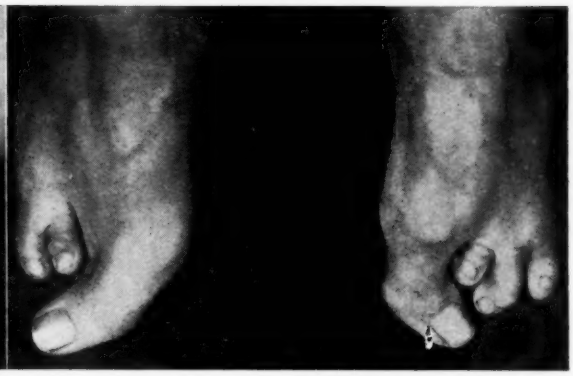

FIG. 4.

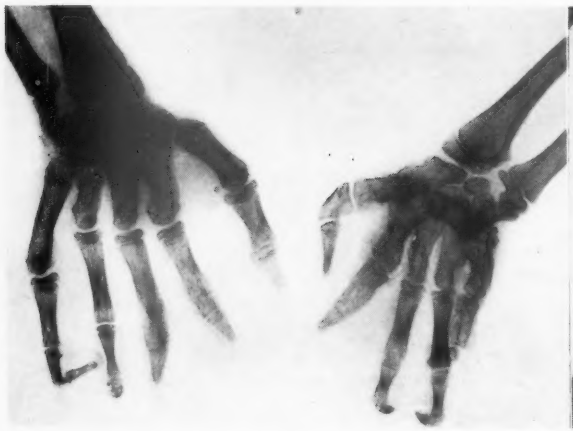

FIG. 5.

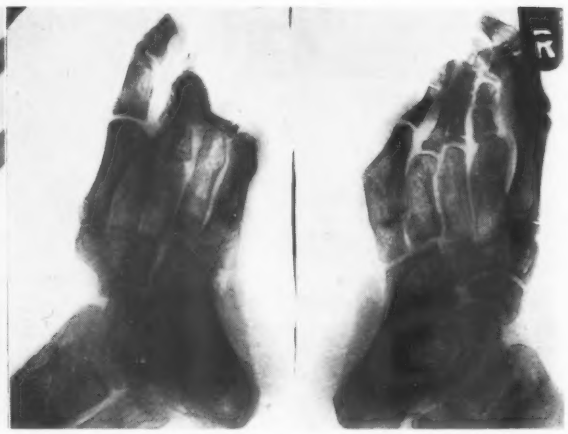

FIG. 6.

underdeveloped. The metatarsals are very broad, barrel-shaped and short. Synostoses between the fifth metatarsal and basal phalanx of the fifth toe, the second cuneiform and the second metatarsal, and talus, calcaneum and cuboid are present.

The left foot shows similar deformities. In addition there is a synostosis involving the third cuneiform and navicular and the second and third metatarsals.

SPINE. The spine shows many features of chondro-osteodystrophy (Morquio), which becomes more pronounced as the years advance. In 1943 there was angular kyphosis in the mid-dorsal region, with wedging of two vertebrae which were smooth in outline and regular in texture. All lumbar vertebrae were a little flat but otherwise of good shape. Because of the dorsal kyphosis the antero-posterior diameter of the chest was large. Findings were hardly characteristic at this stage. The wedged vertebrae and dorsal kyphosis already suggested some developmental abnormality.

By 1950 all the dorsal and lumbar vertebrae had become markedly flat, and their upper and lower terminal plates very irregular in outline. The upper lumbar and lower dorsal vertebrae show the typical beak-like shape of Morquio's disease. Whereas most discs are a little above the normal width, the two lowest discs in the lumbar, and a number in the mid-dorsal, region are narrow or almost absent, indicating that the longitudinal growth of the spine at these levels is about to stop. In the mid-dorsal region there are several almost fully established block vertebrae. This tendency to vertebral fusion clearly distinguishes the findings from those in ordinary Morquio's disease. An unusual lordosis exists in the lower dorsal region (Figs. 7 and 8).

LARGE JOINTS AND LONG BONES. In contrast to the appearances in the spine, the epiphyseal development is generally good and without the features of Morquio's disease. The hips are perfectly normal. So are the epiphyses of the right knee joint. There is a small metaphyseal exostosis at the inner aspect of the right lower femur, the only one found in this case. The left knee shows normal epiphyseal development but a very gross valgus deformity with actual outward subluxation of the lower leg and patella.

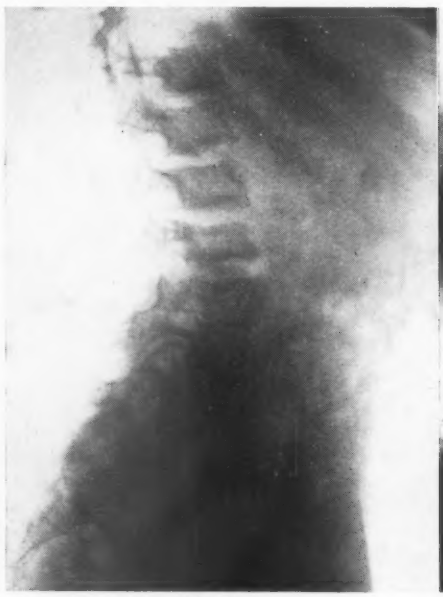

FIG. 7.

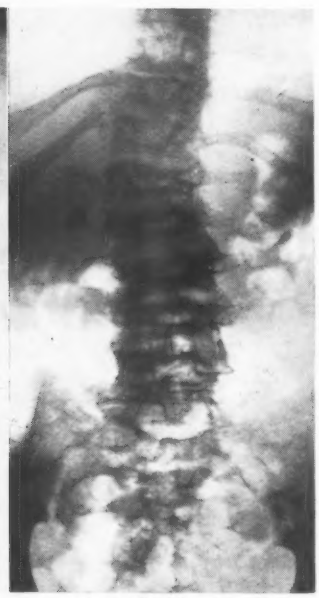

FIG. 8.

The bones of the left leg are atrophic and there are growth lines in femur and tibia. The bones of the lower arms are short and stunted.

SKULL. Findings alter little over the years. The skull is large, with no craniostenosis. The increased space between the orbits (hypertelorism) found on clinical

examination is radiologically very evident. The roofs of the orbits are very much higher than the cribriform plate. There is a steep descent between the floors of the three cranial fossae, a normal sella turcica but rather plump anterior and posterior clinoid processes. The left parietal bone close to the midline shows an area of thinning and outward protrusion (Fig. 9).

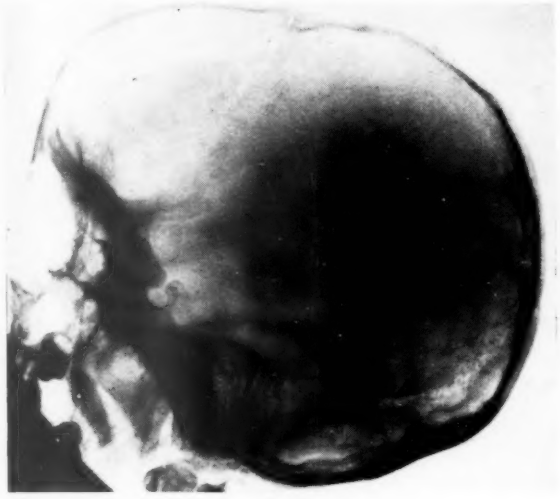

FIG. 9.

Discussion

Holt and McIntosh in 1933 described the case of a 4-year-old girl, born of Jewish parents who were cousins, and exhibiting polydactyly (six fingers, five toes) and skeletal deformity of the achondroplastic type, with irregular and delayed dentition. There was also internal strabismus and calcification in the submaxillary glands.

In 1940 Ellis and van Creveld reported two similar cases and were able to link these with McIntosh's child as examples of a complex syndrome that they described as chondro-ectodermal dysplasia and which has become known as the Ellis-van Creveld syndrome. Both these cases showed, in addition to polydactyly, ectodermal defects, chondrodystrophy, cardiac enlargement and a murmur. The first, a 20-month-old girl, born prematurely of English cousin parents, had dysplastic nails, sparse hair, deficient and prematurely erupting teeth, an achondroplastic skeleton with exostoses of the hips, six fingers and five toes, a systolic murmur and increased transverse diameter of the heart.

The second, a Dutch boy of $4\frac{1}{2}$, had no parental consanguinity. His main abnormalities were deficient and late erupting teeth, dysplastic nails, sparse hair, slow growth, six fingers and five toes, achondroplastic limbs with a large head, a large heart with a systolic murmur, a palpable liver and spleen and undescended testicles.

Since then other cases have been collected (Caffey, 1950; Weller, 1951), and while there are minor variations between them, there is an essential sameness of the main abnormalities. Polydactyly and changes of achondroplastic type are present in all. Ectodermal dysplasia is of the hydrotic type, that is, without disturbance of sweat or sebaceous glands. With the exception of Weller's case the intelligence has been normal.

Weller enlarged the concept of this syndrome to include arthrogryposis of phalangeal joints, and published the case of a 2-year-old Turkish girl who demonstrated all five of the primary abnormalities. In this case the parents were not consanguineous and the child was believed to be mentally backward.

The main difference between our case and those previously reported lies in the nature of the bony abnormalities. In the x-ray analysis of the Ellis-van Creveld syndrome 'the most constant findings are shortening and deformities of the tibia and fibula, and of the radius and ulna, and shortening of the tubular bones of the hands and feet with polydactyly and massive fusion of the carpal bones. . . . The femur and humerus may be bowed as well as shortened. . . . The spine is normal radiologically' (Caffey, 1950). The case here reported, while showing many of the features of the Ellis-van Creveld syndrome, has in addition features of the spinal form of chondro-osteodystrophy (Morquio) associated with a tendency to vertebral fusion.

Unfortunately we lost sight of our patient before a study of the possible heart lesion was complete. Not much significance, therefore, can be attached to the precordial murmur that was audible; with a normal x-ray contour of the heart a congenital heart lesion cannot be substantiated, though it remains a suggestion. From external examination it appears that syndactyly replaces the more usual polydactyly in our case, but a radiograph of the left hand reveals a rudimentary extra digit.

About these differences Ellis (1951) comments: 'I agree that there are several features resembling the cases reported in the *Archives*, but I think one could hardly say it is the same syndrome. Although one would need many more cases and family histories to speak with any certainty, I should rather imagine that these bizarre syndromes are due to a linkage of genes. If this is so, it would explain why your case shows certain features which differ from ours. The osseous dystrophy, for instance, is more similar to chondro-osteodystrophy than it is to achondroplasia, but at the same time there are undoubtedly intermediary types which show features

of both. Similarly there are connecting links between syndactyly and polydactyly, though one is primarily a failure of differentiation and the other reduplication or excessive differentiation. I suppose one might reasonably make some more general description which would cover both groups of cases, particularly if the diastolic murmur in your case could be shown to be due to some congenital defect, as I imagine it must be. Thus both groups show abnormalities of differentiation of the digits, ectodermal defects, osseous dystrophy and cardiac abnormality.'

Of the five basic abnormalities in the Ellis-van Creveld syndrome, therefore (polydactyly, ectodermal defects, chondrodystrophy, congenital morbus cordis, arthrogryposis), this child manifests only the ectodermal defects and arthrogryposis in unmistakable form. The characteristic chondrodystrophy and polydactyly are present in rudimentary form, but combined with other obscuring features. The presence or absence of the fifth element, namely, congenital heart disease, remains uncertain.

Summary

The case of a 12-year-old girl is reported, which exhibits ectodermal defects, spinal chondro-osteodystrophy of the Morquio type and certain other bone and joint deformities.

Resemblances to the Ellis-van Creveld syndrome are discussed.

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TYPHOID OSTEITIS IN INFANCY

BY

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In 1835 Maisonneuve first recognized osteomyelitis as a complication of typhoid and since then this bone lesion, although well known, has been reported only occasionally. Murphy (1916) collected 164 cases of typhoid periostitis and osteitis occurring in 18,840 cases of typhoid infection reported by 15 authors, an incidence of 0·82% of bone involvement. Veal (1939) also found osteitis in less than 1% of typhoid infections.

In discussing the age incidence Murphy (1916) reported six cases (0·9%) of typhoid periostitis occurring in the age-group 1 to 10 years in a total of 68 cases at all ages. By comparison, in a series of 411 cases of septic osteomyelitis at all ages he found 108 (26%) in the first decade. Winslow (1923) found 101 proven cases in the literature and he added two of his own. Four of these occurred in the first decade, the youngest being 2 years old. Of this series 68 had one and 23 had two bones involved. Veal (1939) also recorded multiple bone involvement in less than 5% of cases. Typhoid lesions tend to remain localized in contrast to paratyphoid B infections which tend to spread through the length of the bone. Webb-Johnson (1917) illustrated the extreme rarity of bone involvement in paratyphoid B infections, recording only two instances in a study of 1,038 examples of this disease.

There may be a wide variation in the latent period between the acute illness and the subsequent bone involvement. In Winslow's 101 cases the bone manifestations occurred during the acute attack in nine, at an unspecified date during convalescence in 53, and months or years after convalescence in 20 cases. The tibia appears to be the bone most commonly affected. Morse and Geiser (1950) reported a case of typhoid osteomyelitis treated with chloramphenicol.

Typhoid bone lesions are extremely rare in infancy and we wish to record two cases.

Case Reports

Case 1. W.R., a boy 6 months old, was admitted to hospital on April 3, 1951. He had had a pyrexial illness for 17 days before admission. Four days after the onset he developed a macular skin eruption suggestive of a 'rose' rash. For six days he was treated with sulphadiazine and penicillin, when the pyrexia subsided. After another six days it was noticed that the infant resented any interference with the left shoulder, apparently due to pain. Four days later the right shoulder became affected and he was admitted to hospital. In the four days before admission he again became pyrexial.

The pregnancy and labour were normal and the parents and one sibling were healthy. The birth weight was 7 lb. 6 oz. and there had been no illness before the present one. He had been vaccinated two months, and immunized against pertussis one month before admission.

On examination he appeared a well nourished infant weighing 19 lb. 10 oz. The temperature was 101° F., pulse rate 124 per minute, respiration 26 per minute. Nothing abnormal was detected in the cardiovascular, respiratory or central nervous systems. The liver and spleen were not palpable. The child resented handling of both shoulders. He would not move his arms and this refusal appeared to be due to pain and not to muscular weakness. There were palpable lymph nodes in both axillae.

INVESTIGATIONS. A blood count gave: haemoglobin, 9·4 g. %; colour index, 0·87; erythrocytes, 3,500,000 per c.mm.; leucocytes, 13,700 per c.mm. (neutrophils, 55%, monocytes, 3·5%, lymphocytes, 41%, eosinophils, 0·5%). The sedimentation rate was moderately increased. The cerebrospinal fluid was normal. The Wassermann reaction of both cerebrospinal fluid and blood was negative. Blood culture in broth and bile grew no bacteria. No pathogenic bacteria or animal parasites were isolated from the stool on repeated examination. The urine contained no albumin, sugar or acetone and *S. typhi* was not isolated from the urine. The Mantoux reaction was negative. *S. typhi* was not isolated from a sternal marrow culture. The agglutination reaction for *S. typhi* 0 antigen was positive at a titre of 1 in 800, with a trace at 1 in 1,600. This was obtained 17 days after admission to hospital. A further positive reaction to the same antigen in a titre of 1 in 400 was obtained a month later. Agglutination reactions for *S. typhi* H and Vi were negative, as were those for *S. paratyphi* A, B and C, and *Brucella abortus* and *melitensis*. The intracutaneous Brucella skin test yielded a negative result.

RADIOLOGICAL EXAMINATION. Radiographs of both shoulders taken three days before admission to hospital

were normal. Two days after admission the right shoulder was still normal, but on the left the deltoid region was swollen, with oedema of the musculo-subcutaneous plane (Fig. 1), and there was a narrow band of rarefaction in the metaphysis of the head of the humerus parallel to the epiphyseal line. There was also swelling of the lymph nodes in the axilla.

FIG. 1A FIG. 1B

FIG. 1.—(Case 1, 5.4.51.) Radiographs taken on April 4 showing right shoulder radiologically normal; left shoulder with soft tissue swelling of the deltoid region, oedema of the musculo-subcutaneous plane, enlargement of the axillary lymph nodes and a band of minimal (not reproducible) rarefaction in the metaphysis.

On the following day this area of rarefaction was larger and more irregular (Fig. 2) and there was a similar area in the head of the right humerus. One week later the lesion in the right head was more obvious (Fig. 3) and that in the left was a little larger and better defined. After a further week marginal sclerosis could be detected about the area of erosion on both sides and there was bilateral minimal subluxation. At the end of the sixth week these changes were well developed (Fig. 4). During the next month the area of sclerosis gradually encroached on the area of rarefaction, which on the right side developed a coarse trabeculation (Fig. 5), while the epiphyses of the head became smaller and almost completely disappeared. Thereafter the lesions became more sclerotic and the epiphyses reappeared in a fragmented fashion suggesting ossification in multiple centres. On the right side the epiphysis of the greater tuberosity appeared prematurely. The subluxation on the right disappeared but it persisted on the left side.

This infant presented with an acute pyrexial illness associated with a rose-rash suggesting an acute typhoid infection. It was soon followed by involvement of the left and then the right shoulder, causing pain and immobilization at these sites. The radiological examination at first suggested an acute metaphyseal osteitis, but the subsequent course was unusually slow. The epiphyseal changes were due to direct invasion or to avascular necrosis consequent upon the metaphyseal involvement or to hyperaemia. The first was thought to be the more likely as avascular necrosis following infection usually leads to complete resorption or extrusion of the epiphysis and reossification after hyperaemia is not multicentric. It cannot be determined without aspiration, which was not performed here, whether the joint was actually

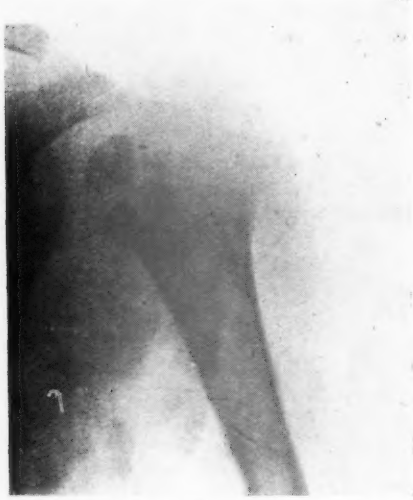

FIG. 2.

FIG. 2.—An increase in size and irregularity of the area of rarefaction is seen in the left metaphysis on April 6. The musculo-subcutaneous plane is now well defined. A similar but less marked area of rarefaction on the right side could not be reproduced.

FIG. 3.—The area of rarefaction in the right head is now (April 12) clearly visible.

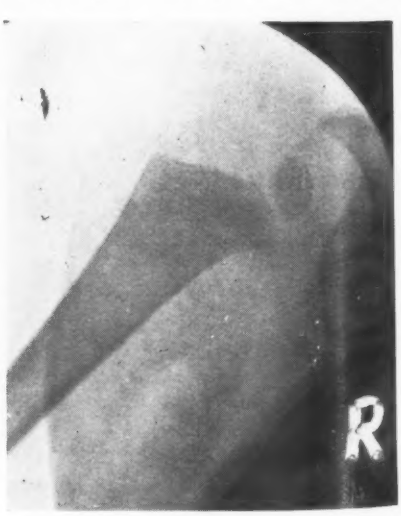

FIG. 3.

infected or not. The initial blood count showed an anaemia with a neutrophilia, and the diagnosis of typhoid osteitis was determined by the initial illness and the positive agglutination reactions to *S. typhi* 0 antigen in titres of 1 in 1,600 and 1 in 800. A diagnostic titre for this antigen for the Witwatersrand area, where this case occurred, has been determined by Lewin (1938) to be 1 in 200.

This child had two courses of chloramphenicol therapy, in a dosage of 250 mg. every six hours first for 13 days, and subsequently for 11 days.

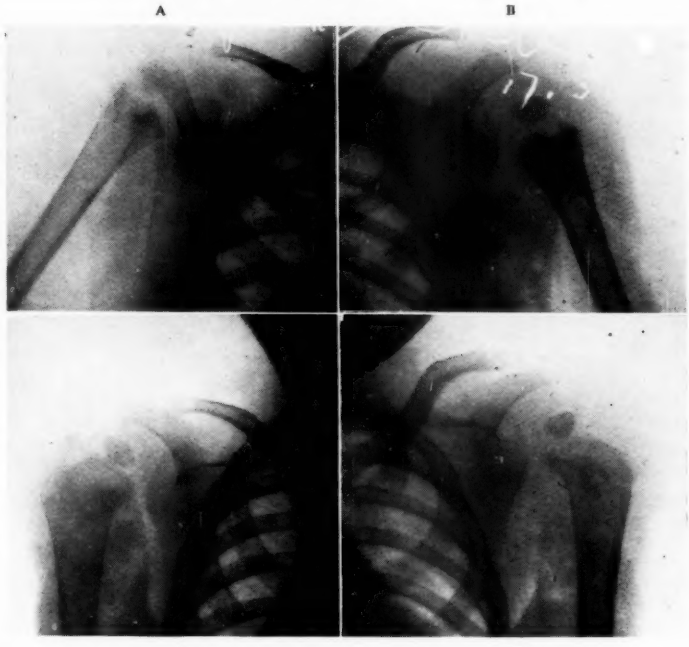

FIG. 4.—Radiograph on May 17 showing gross destructive changes with irregularly sclerotic margins in the metaphyses and minimal subluxation of the head on both sides.

Case 2. A.M., a girl 10 months old, was admitted to hospital on August 15, 1951. She had been perfectly well until three weeks before admission. She then developed a fever and would not move the left arm. The temperature remained raised for two weeks during which time she still would not move the arm. She was born normally at term after a normal pregnancy. The parents and six siblings were all well.

On examination the patient was seen to be a well nourished infant weighing 18 lb. The temperature was 98° F., the pulse rate 110 per minute and respiration 26 per minute. Nothing abnormal was detected in the cardiovascular, respiratory or central nervous systems. The spleen and liver were not palpable. There was a hot, tender swelling of the upper half of the left arm. Movement at the shoulder was resisted because of pain. There was full movement of the elbow and wrist, and the other limbs were normal.

INVESTIGATIONS. A blood count gave: haemoglobin, 9·9 g. %; colour index, 0·92; erythrocytes, 3,500,000 per c.mm.; leucocytes, 8,400 per c.mm. The red cells showed anisocytosis. The sedimentation rate was 60 mm. in one hour. The packed cell volume was 30%. The modified Ide test and the Mantoux reaction were negative. The cerebrospinal fluid was normal. Agglutination tests for *S. typhi* 0 showed a positive reaction in a serum dilution of 1 in 25 and a doubtful reaction in a dilution of 1 in 200. This test was repeated after a week and a positive reaction was obtained at a titre of 1 in 800.

RADIOLOGICAL EXAMINATION. On the day of admission radiographs of the left shoulder showed soft tissue swelling with oedema of the musculo-subcutaneous plane. The epiphysis for the greater tuberosity on this side was not visible. There was a band of rarefaction in the metaphysis. Three days later the soft tissues appeared normal, and the area of rarefaction was more clearly defined (Fig. 7). Seventeen days later the area of rarefaction was slightly larger and better defined, with a linear sclerotic margin. There was also a minimal periosteal reaction. After a further 18 days the erosion was smaller, the area of sclerosis had increased and the periosteal reaction had subsided. Finally, three and a half

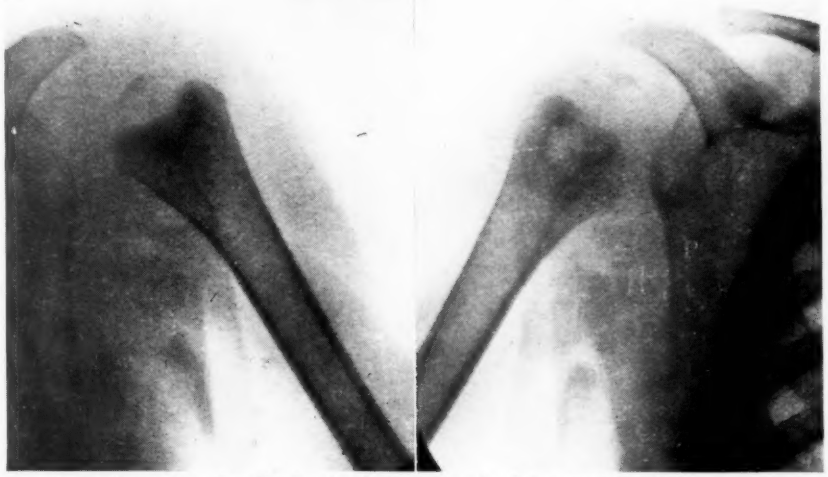

FIG. 5.—Radiograph on June 28 showing further sclerosis of the margins of the areas of erosion. On the left it is encroaching on the area of destruction. On the right the area of rarefaction is becoming coarsely trabeculated. The subluxation persists. Note almost complete disappearance of epiphyses of heads.

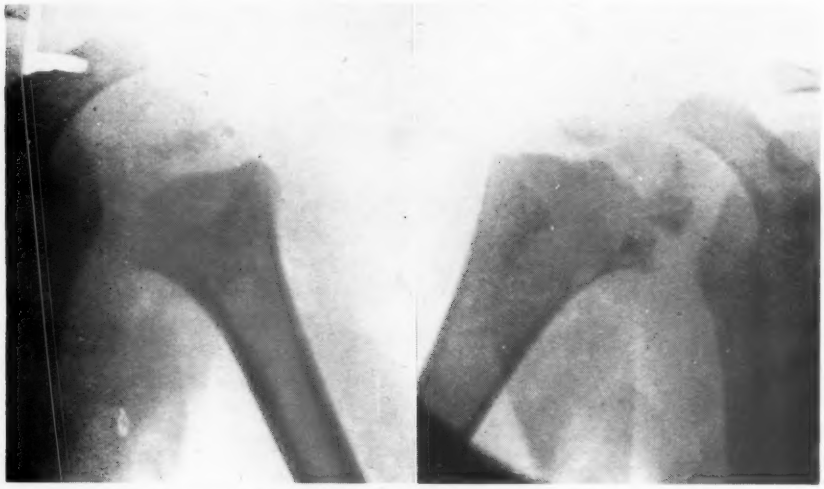

FIG. 6.—Radiograph on November 19, 1951. The areas of erosion are now completely recalcified. On the left the sclerotic margin is less evident and on the right there is no sclerosis. Note the coarse trabeculation, more marked on the right. Note also the fragmentation of the epiphyses, and the early appearance of the epiphysis for the greater tuberosity on the right. Subluxation is still evident on the left.

months after the initial examination, there was complete restitution to normal.

This infant presented with a pseudo-paralysis of the left arm. Neither the mother nor the child had had T.A.B. vaccine injections or obvious enteric fever. The child had anaemia and the diagnosis of typhoid osteitis was suggested from the radiograph which closely resembled that of Case 1, and it was confirmed by the rise in titre of the agglutination reactions. Chloramphenicol was given in a dosage of 250 mg. every eight hours for 12 days. The subsequent radiological examination showed a regression with a tendency to healing. The final radiograph showed complete restitution to normal.

Discussion

Both these infants, a boy and a girl, were under 1 year of age. In the first the diagnosis was suggested by the clinical history, the failure to respond to penicillin, the unusually slow course of the lesions as shown radiographically and the positive agglutination reactions in extremely high titre. In the second case the close resemblance of the initial radiograph to that of the first patient raised the suspicion of a similar aetiology, and the high and rising titres of the agglutination reactions confirmed this. Both presented with pseudoparalysis, one bilateral, and with pyrexia. Both were anaemic, and one had an initial neutrophilia with a total leucocyte count of 13,700 cells per c.mm. Both were treated with chloramphenicol. The second patient, with the single lesion, in whom the diagnosis was made earlier in the course of the disease, showed complete resolution of the lesion in three and a half months, but in the first child there was still evident deformity without disability after eight months, suggesting that early effective treatment prevented irreversible changes in the bone in the second case.

The question arises whether there is anything characteristic about the bone lesions that should arouse suspicion and so lead to earlier diagnosis. The oedema of the musculo-subcutaneous plane is a well known early manifestation of osteitis, and it was the first sign in two of these three affected shoulders, although it was not observed in the right shoulder in Case 1. Such localized oedema in the absence of direct trauma or an injection is suggestive of acute osteitis. It has not been reported in congenital syphilitic lesions, which had to be considered here once the metaphyseal rarefaction became visible. However, at the stage at which syphilis produces a pseudoparesis it almost invariably also causes a well marked periosteal reaction, with a metaphyseal notch and epiphyseal displacement. The distribution of the lesions and the serology also excluded syphilis. Tuberculous osteitis also was considered, but both the course of the lesions and their appearance were unlike tuberculosis which readily

FIG. 7.—Radiograph (Case 2) on August 18 showing area of rarefaction in the metaphysis on the left side. The soft tissues at this stage appeared normal.

crosses the epiphyseal line or, in infants, spreads to the joint with gross destruction. The negative Mantoux reaction was regarded as conclusive in this respect. Pyogenic osteitis could not be excluded initially, but it was thought unlikely in the absence of clinical response to penicillin and of periosteal reaction in the presence of marked destruction in the medulla. It is therefore suggested that a pseudoparesis associated with a subacute bone lesion resembling an acute osteitis, but taking a slower course and showing little periosteal reaction, should arouse a suspicion of typhoid infection.

Summary

Two cases of typhoid bone lesions in the first year of life are reported. The metaphysis of the upper end of the humerus was affected in both cases. In one case the lesion was bilateral, in the other unilateral. One case also developed bilateral osteochondritis, osteitis or hyperaemic deossification of the epiphyses, with subsequent reformation and slight deformity. The other case, diagnosed earlier, showed complete return to normal. Chloramphenicol therapy was used in both cases. The literature is briefly reviewed.

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A CASE OF OSTEOMYELITIS OF ALL THE SMALL BONES OF THE HANDS AND FEET

BY

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Osteomyelitis is not a rare disease in infants, often involving multiple sites, particularly in the newborn, but no case parallel to that about to be described has been found after a careful search of the literature.

Green and Shannon (1936), reporting 95 cases of this disease in children under 2 years of age treated at the Children's Memorial Hospital, Boston, during the years 1925-36, showed that while the usual conception of staphylococcal bone infection is true in older children, the streptococcus is more commonly the causative organism in infants. In their series 63% of cases were due to streptococci. There was a striking relationship to antecedent infection, mainly respiratory (50%) and cutaneous (25%), and streptococcal osteomyelitis was particularly prevalent in cases with a history of recent respiratory infection. In pre-penicillin days mortality was high, being 21% overall in this group, but 45% in children under 6 months of age. The prognosis for sound bones, provided the patient survived the acute stage, was, however, shown to be good. Wade (1929) mentions the frequency of streptococcal and pneumococcal infections of bone in his series of infants under 3 months of age.

Infants have a natural method of decompression of the marrow space, as cortical bone is especially thin at the metaphysis, which is ordinarily the site of infection. Secondary abscesses under the periosteum are therefore common and sequestration is rare, but the proximity of the metaphyseal line to the capsule of most joints makes pyarthrosis a common complication. Even this complication appears to carry a good prognosis except when it occurs in the hip. Multiple sites of infection are mentioned by Einstein and Thomas (1946), Green and Shannon (1936) and Wade (1929), the last author describing infection in tarsal bones, but metatarsals and metacarpals seem rarely to be involved.

Case History

D.G. was admitted on October 15, 1949, at the age of 15 months with a history of fever, malaise and vomiting of two days' duration. She was the third child of healthy parents, born at full term. Her birth weight was 8 lb. 11 oz. She had been breast fed and had developed normally, but was not yet walking. Her previous history had been uneventful except for eczema in early infancy. The child's mother had had a sore throat a few weeks before the patient's admission, but the rest of the family were quite healthy.

Examination revealed a feverish, toxic child, sleeping when left undisturbed (temperature 101° F., pulse 136, respirations 26). The tonsils were enlarged and injected, but free from exudate and there was little swelling of the tonsillar glands. There was no stiffness of the neck and Kernig's sign was negative. Heart, lungs and abdomen were normal, but over the shins were several tender, indurated, purplish nodules. A similar lesion was seen near the right elbow, and a diagnosis was made of streptococcal tonsillitis with erythema nodosum. A throat swab and blood culture were taken and penicillin therapy started.

On the day after admission the patient's hands and feet were noticed to be swollen (Fig. 1) and on October 17

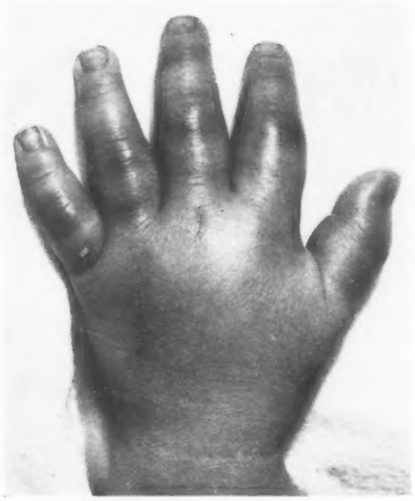

FIG. 1.—The left hand three days after the onset.

there was definite oedema of the extremities without puffiness of the face or pitting in the sacral region. The

urine contained a trace of protein, but no cells or casts, and the systolic blood pressure was only 92 mm. The throat swab taken on admission was reported negative for haemolytic streptococci and a blood count showed only a slight leucocytosis: Hb. 70%; leucocytes 10,200 (polymorphs 71%, lymphocytes 26%, monocytes 3%). A tuberculin jelly test was negative. By October 19 the child was apyrexial, looked better, the hands and feet were less swollen and the erythematous blotches were fading. A radiograph of the extremities was normal. Penicillin therapy was stopped at this point, and salicylates given together with antihistamine drugs, as a diagnosis of acute rheumatism was now entertained. However, by October 21 her temperature had again risen, this time to 103° F., and the following day the blood culture was reported positive for haemolytic streptococci. Blood was again taken for culture and penicillin therapy started again. The tip of the spleen became palpable on October 27 and blebs appeared on the swollen fingers and right foot on November 3 but the patient's general condition improved slowly. A little bloodstained fluid aspirated from the subcuticular lesions was sterile on culture, but contained a moderate number of polymorphs. The second blood culture taken October 21 was reported positive for haemolytic streptococci group A on November 1. The extremities were radiographed again on November 4, and multiple areas of destruction were seen in all the phalanges and metacarpals of both hands. There was also a little periosteal proliferation and medullary translucency in several metatarsal bones with irregularity of terminal phalanges in the feet. A moderate leucocytosis (leucocytes 14,500, with 71% polymorphs) was now present. The blood Wassermann reaction was negative. On November 9 erosion of the distal half of the shaft of the left ulna was apparent radiologically, and patchy rarefaction of phalanges particularly at the metaphysis made the diagnosis of multiple foci of osteomyelitis incontrovertible (Fig. 2). Penicillin therapy was continued and from November 11 the child was apyrexial. Swelling of the hands and feet subsided gradually and by December 6 she was willing to move her hands a little. Antibiotic therapy was discontinued on December 22 after 32 days' continuous treatment. By January 1, 1950, she was able to stand with support and the hands and feet were quite mobile, but the small bones felt enlarged. Radiographs showed new bone formation following rarefaction and fragmentation, but the os magnum, which had previously been visible in both hands, appeared to have been absorbed. No sequestra were seen. The child was discharged on January 2 and further observation in the out-patient department showed steady clinical and radiological improvement (Figs. 3 and 4). She started to walk in May, 1950, at 22 months, and was able to run and jump by 3 years, clumsily at first but quite nimbly later. By July, 1950, the carpal and phalangeal epiphyses were appearing and further improvement in the shafts of the phalanges was seen, although areas of translucence persisted causing a cystic appearance. This change had disappeared by March, 1952. Her subsequent progress has been normal, and she is now free of symptoms and signs.

Summary

A case of osteomyelitis involving all the small bones of hands and feet and one ulna in a child of 15 months is described. No similar case has been found in a search of the literature. With prolonged penicillin therapy, and without recourse to surgery, the patient recovered completely.

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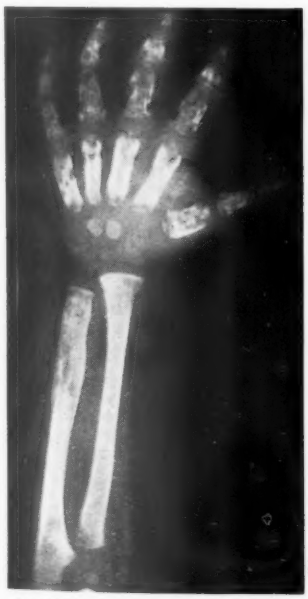

FIG. 2.

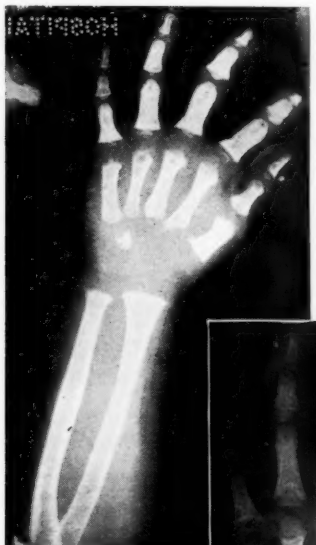

FIG. 3.

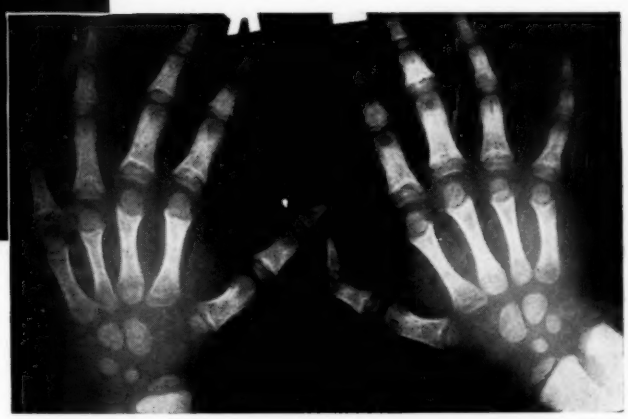

FIG. 4.

FIG. 2.—Radiograph five weeks after the onset, showing osteomyelitis of the ulna, metacarpals and phalanges.

FIG. 3.—Radiograph 20 weeks after the onset, showing carpal absorption with improvement in other bones.

FIG. 4.—Radiograph of hands showing restitution two years and five months after the onset.

ACCIDENTAL POISONING OF YOUNG CHILDREN

BY

DOUGLAS SWINSCOW

(RECEIVED FOR PUBLICATION OCTOBER 8, 1952)

Deaths from violence constitute the largest single group of deaths to which children aged 1-4 fall victim. The accidental ingestion of poisonous substances is a small but important cause of these deaths. During the decade 1940-49 the Registrar General for England and Wales reported the deaths of 218 children aged 1-4 from accidental poisoning other than by toxic gases. An account of the substances causing these deaths seemed to be worth while, since they have not previously been recorded.

Fig. 1 illustrates how children aged 1-4 are particularly liable to death from accidental poisoning. (In this paper the phrase 'accidental poisoning' means poisoning by ingestion of toxic substances, and the deaths referred to are those given by the Registrar General under the heading 'Other Acute Accidental Poisoning (not by Gas)', International List No. 179). In Fig. 1 the broken line shows the annual average death rate at age groups (without distinction of sex) for 1931-39 and the continuous line the same for 1940-49. Though the death rate in 1940-49 appears to be higher at every age group than in 1931-39, the disparity may be wholly due to the differences in recording the statistics, since from 1940 onwards deaths from accidental poisoning on which coroners' open verdicts were given were assigned to this category instead of to a separate one.

A detailed analysis of the average annual death rates at age groups in the two sexes is given in Table 1 for the two periods of years 1931-39 and 1940-49.

It shows that the death rates of both males and females follow similar trends, and that the death rates of children up to the age of 5 are considerably greater for boys than for girls. The disparity between the sexes is greater for these death rates than it is for the death rates calculated from all other deaths combined. The ratios of male death rates as a

TABLE 1

AVERAGE ANNUAL DEATH RATE PER MILLION FROM ACCIDENTAL POISONING AT AGE GROUPS, SEXES DISTINGUISHED, FOR 1931-39 AND 1940-49

Age in Years	1931–39			1940–49		
	Males	Females	Total	Males	Females	Total
Under 1	2·6	1·6	2·1	3·7	2·1	2·9
1–	6·1	4·7	5·4	9·9	7·5	8·7
5–	0·5	0·6	0·5	0·9	0·9	0·9
10–	0·5	0·1	0·3	0·6	0·4	0·5
15–	0·5	0·5	0·5	1·5	0·7	1·1
20–	1·3	0·9	1·1	3·0	1·8	2·2
25–	1·6	1·2	1·4	3·3	2·4	2·8
35–	2·2	2·1	2·2	3·7	3·3	3·5
45–	3·4	3·3	3·3	6·0	4·6	5·3
55–	4·9	3·1	4·0	4·7	5·2	4·9
65–	5·3	3·3	4·2	6·7	5·9	6·2
75+	6·8	6·0	6·3	7·6	6·0	6·6

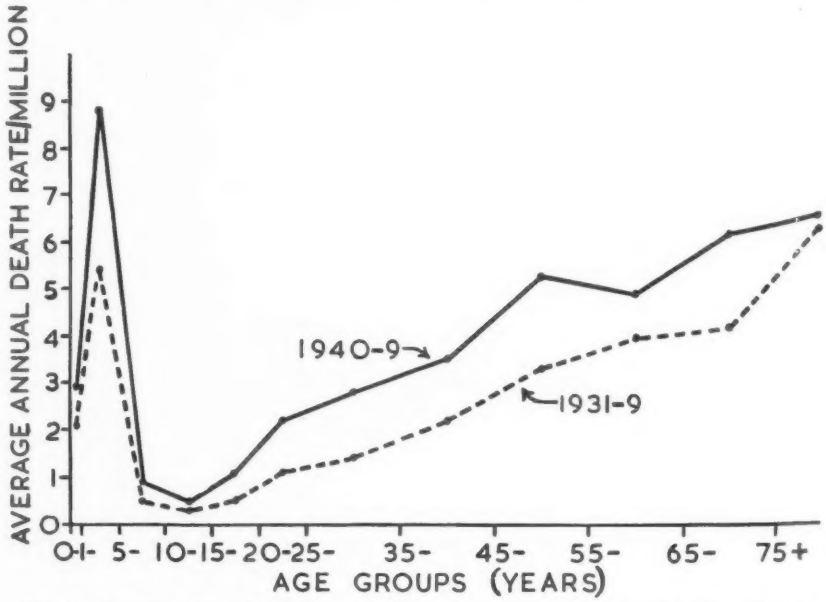

FIG. 1.—Average annual death rate per million, at age groups, for the two periods 1931-39 and 1940-49.

percentage of female death rates illustrate this in Table 2.

TABLE 2

MALE DEATH RATES AS PERCENTAGES OF FEMALE DEATH RATES FOR ACCIDENTAL POISONING AND FOR ALL OTHER CAUSES OF DEATH COMBINED

Age Group	Accidental Poisoning		All Other Deaths	
	1931–39	1940–49	1931–39	1940–49
Under 1 ..	169	177	131	130
1–4 ..	130	131	111	115

An explanation for the disparity can be found if it is true, as is widely believed, that boys are more exploratory than girls. Certainly males are in general much more liable to injury in the home than females (Lockhart, 1950).

In the decade 1940-49 the average annual death rate per million from accidental poisoning was 8·7 for children aged 1-4. The rates for the three most recent years were slightly above the average, but, as the following annual rates for each year successively in the decade show, there is no firm evidence of a continuing rise: 8·7, 8·7, 8·8, 6·2, 6·4, 10·3, 7·0, 10·9, 9·4, 10·1.

Types of Poison

Records of the poisons stated to have caused the deaths of children aged under 15 were obtained from the Registrar General for England and Wales. Since the hazard is so much less for children older and younger than those aged 1-4, the deaths of children only in the last age group are discussed below. An attempt was made to classify initially into broad groups the remarkably varied collection of poisons that caused their deaths, and five main groups can be defined as follows.

(1) **Medicaments.** These are preparations prescribed by doctors or bought at chemists by patients for therapeutic purposes, to be taken internally or applied externally.

(2) **Disinfectants and Antiseptics.** These are nearly all phenol and cresol preparations, though inhalants containing these may have been the true origin, in which case some or all should be classified under medicaments.

(3) **Household Poisons.** This category comprises poisons commonly used in houses and gardens for purposes other than medication or disinfection, e.g. rat poison, insecticides, turpentine.

(4) **Poisonous Plants.**

(5) **Miscellaneous.** The contents of this category arrive here by exclusion from others. Most of them are poisons sometimes kept at home but not often, e.g., hydrochloric acid (possibly for soldering), chromates, methyl alcohol.

While lack of explicit information makes assignment of any particular poison to its correct group occasionably debatable, there are too few doubtful cases to invalidate the broad classification.

Table 3 shows how the poisons fall into these categories. It will be seen that medicaments in both periods comprise much the largest groups, 52% in 1931-39 and 62% in 1940-49. The difference of 10% between the two periods is not statistically significant (S.E. of difference=5·7), nor does the distribution of deaths in the 1931-39 totals differ significantly from the distribution in the 1940-49 totals ($\chi^2=4·721$, $P>0·3$). In other words, in the two periods the proportion of deaths in each group is much the same.

Medicaments

It now remains to record in more detail the substances that poisoned these children aged 1-4, and to consider first the medicaments. Here rather more guesswork accompanies the classification because of the scanty information registered.

An important group in both 1931-39 and 1940-49 is the liniments, causing 13 out of 58 deaths (22%) in the first period and 29 out of 135 (21%) in the second. Many of these are attributed to oil of

TABLE 3

NUMBERS OF DEATHS FROM ACCIDENTAL POISONING OF CHILDREN AGED 1-4 YEARS GROUPED BY TYPE OF POISON

Group of Poisons	1931–39			1940–49			% of Cases in Groups	
	M.	F.	Total	M.	F.	Total	1931–39	1940–49
Medicaments	31	27	58	71	64	135	52	62
Disinfectants and antiseptics	3	4	7	11	4	15	6	7
Household poisons	18	11	29	31	16	47	26	22
Poisonous plants	4	4	8	6	2	8	7	4
Miscellaneous	8	2	10	7	6	13	9	6
Total	64	48	112	126	92	218	100	101

wintergreen, bottles of which probably repose unguarded in many homes. The actual figures are as follows:

Deaths from:	1931–39	1940–49
Oil of wintergreen	6	17
Camphor or camphorated oil	6	5
Camphor and wintergreen	1	–
A.B.C. liniment	–	1
Methyl salicylate	–	5
Not stated	–	1

With these may be mentioned one death from salicylate and one from salicylic acid in 1931-39.

Another prominent though more varied group comprises deaths due to iron and/or strychnine preparations, many of which are probably taken for diagnosed iron-deficiency anaemias or as tonics, though the strychnine in some cases may have come from aperient pills. These cases numbered 19 (33%) in 1931-39 and 36 (27%) in 1940-49. The details are as follows:

Deaths from:	1931–39	1940–49
Iron preparations	2	21
Easton's syrup or tablets	10	–
Strychnine	6	15
Nux vomica and belladonna	1	–

Anodynes caused a number of deaths in both periods: five (8·6%) in 1931-39 and 23 (17%) in 1940-49. These comprised the following:

Deaths from:	1931–39	1940–49
Aspirin	3	12
Opium or morphine	1	8
Chlorodyne	1	1
Diamorphine	–	2

Quinine preparations (apart from Easton's syrup) caused four deaths in the first period and 12 in the second, digitalis preparations three and four, and hyoscyamine three in the second period only.

Two important groups of drugs caused deaths in 1940-49 only; these were antihistamines and soporifics. Three deaths were attributed to an unspecified antihistamine, one to 'benadryl' and one to pyranisamine maleate. Of the eight deaths due to soporifics, six were caused by phenobarbitone, one by chloral hydrate and one by unspecified sleeping tablets.

Medicaments which were presumably aperients caused two deaths in the first period and two in the second; in the former two cases the drugs contained colocynth and in the latter two aloin.

The remaining preparations that caused deaths in either of the two periods were the following: ipecacuanha, one; acetic acid, four; lethane, four; antimony, one; copper sulphate tablets, one; hydrocyanic acid, one; iodine, one; a tar preparation, one; and unspecified pills and tablets, two.

Disinfectants and Antiseptics

Phenol and cresol (or its allies) have been included under this heading, though it is possible that some of the deaths were due to drinking inhalants containing creosote.

The preparations in this group caused the seven deaths in 1931-39. They were also responsible for nine of the 15 deaths that occurred in 1940-49; of the remaining four deaths, three were attributed to potassium permanganate and one to mercury perchloride.

Household Poisons

Prominent among these as a cause of death is caustic soda. It was responsible for nine out of 29 deaths in this group in 1931-39 and for 12 out of 47 in 1940-49, when caustic potash also caused a death. About equally dangerous is phosphorus in its various forms, causing six deaths in the first period and 11 in the second; most of these were due to rat poison. Paraffin, kerosene, turpentine and petrol accounted for 15 deaths between them in the two periods, ammonia for five, and nicotine (presumably as insecticide) for four; arsenic as either a rat poison or a weed killer caused three, as did metaldehyde (used as a fuel or a slug poison). The remaining deaths in this group were due to creosote (possibly a 'medicament'), one; oil of citronella, one; carbon tetrachloride, one; oxalic acid, one; and some incompletely specified substances, three.

Poisonous Plants

Out of the 16 deaths during 1931-49, eight were caused by deadly nightshade and three by woody nightshade. The remaining deaths were due to privet berries, one; water dropwort, one; hemlock, one; fungi, one; and unspecified berries, one.

Miscellaneous Group

Hydrochloric acid, including soldering fluid, was the chief cause of death in this varied group of poisons, being responsible for six of the 23 during 1931-49. Others included potassium chromate or bichromate, four; sulphuric acid, two; methyl alcohol, one; and potassium sulphide, one.

Discussion

Probably something over 5,000 fatal accidents occur in the homes of England and Wales every year (Registrar General, 1951), and it is often difficult to determine the cause for the recorded death. The facts set out above have therefore been given in some detail in an attempt to elucidate the causes of a small group of these accidents and to contribute towards their prevention. Representatives of the General Medical Services Committee of the B.M.A. and of

the Pharmaceutical Society have exchanged preliminary views on how to prevent the poisoning of children by medicaments, and an interdepartmental committee set up by the Home Office exists to study the causes of accidents in the home.

In spite of the impossibility of classifying some of the poisons because of incomplete information, there can be no doubt that most of these deaths are caused by medicaments, an observation borne out by Holzel and James (1951) in their study of some cases of accidental poisoning admitted to a Manchester hospital. Drugs and other medical preparations are left in reach of children, who imitate their parents in consuming them. The variety of substances taken suggests that taste can hardly be the attraction in many cases, and merely refraining from prescribing medicines and tablets in a form pleasing to the palate is unlikely to prevent many accidents, though it may be a wise precaution. Spencer (1951) has suggested wrapping single tablets or small groups of them in paper so that they are difficult to undo, and this might be an effectual preventive, albeit expensive.

What these notes show clearly is, first, the special danger to pre-school children of accidental poisoning (also emphasized by Holzel and James, 1951); secondly, that many of the preparations causing death are not generally regarded as dangerous poisons; thirdly, that the preparations are in the main those found very commonly in homes; and, fourthly, that most of these dangerous preparations are medicaments.

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Doctors often warn parents to keep some drug away from children; that their advice should sometimes fail is natural. But it may be doubted whether either doctors or parents are sufficiently aware of how dangerous to children, and how attractive, are many medicaments which, commonly prescribed or bought, are harmless to adults even in large doses. Nor are doctors the only people who might warn members of the public more often. They should surely be joined by the manufacturers, who could label preparations more prominently as poisons, and chemists and ironmongers have an important duty to emphasize the special danger to children of many of the substances they sell.

Summary

Accidental poisoning by ingestion of toxic substances, especially medicaments, is a notable cause of death in the age group 1-4 years.

The poisons causing the deaths of children in this age group in England and Wales during 1931-49 are recorded.

It is not sufficiently realized (what the detailed records show) that many of the medicaments causing death are commonly found in homes and are regarded as harmless to adults in large doses.

I am much obliged to the Registrar General for England and Wales for supplying me with records of poisons that caused the death of children during 1931-49.

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THE SENSITIVITY TO ANTIBIOTICS OF STRAINS OF *BACT. COLI* ASSOCIATED WITH INFANTILE GASTRO-ENTERITIS

BY

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Various workers (Bray, 1945; Giles and Sangster, 1948; Taylor, Powell and Wright, 1949; Rogers, Koegler and Gerrard, 1949; Beeuwkes, Gijsberti Hodenpijl and Ten Seldam, 1949; Giles, Sangster and Smith, 1949; Smith, 1949; Magnusson, Laurell, Frisell and Werner, 1950; Kirby, Hall and Coackley, 1950; Smith, Galloway and Speirs, 1950; Kauffmann, 1950; Neter and Shumway, 1950; Taylor, 1951; Rogers, 1951; Drimmer-Herrnheiser and Olitzki, 1951; Orskov, 1951; Braun and Henckel, 1951; Modica, Ferguson and Ducey, 1952; Shanks and Studzinski, 1952; and Laurell, 1952) have shown that in Great Britain, Denmark, Sweden, Holland, Germany, Palestine and the U.S.A. certain specific serological types of *Bact. coli* can be isolated from the faeces of cases of infantile gastro-enteritis, of which epidemiological evidence suggests they may be the cause. In fact a recent editorial article in the *Lancet* (1952) summarizing the position as regards the 0111 B4 type states that there is now good evidence that the 0111 B4 type of *Bact. coli* may cause infantile gastro-enteritis both as a sporadic and an epidemic disease.

These organisms have been described under various names, but where possible, they have now been classified in the Kauffmann (1947) schema according to their antigenic structure as follows:

Type	Sub-types Described
First type 0111 B4	H– non-motile H2 sucrose-positive H12 sucrose-negative H7 H10 H26
Second type 055 B5	H2 H6 H7
Third type 026 B6	H– non-motile H11
Taylor's types not yet classified serologically	Vincent E611 E990

Several papers have been published (Magnusson *et al.*, 1950; Rogers *et al.*, 1949; Neter and Webb, 1951; Lowdon and McNeill, 1951; Alexander, Benjamin, Maslen and Roden, 1952) on the results of antibiotic therapy in this disease. Some workers have found certain antibiotics gave, clinically, some benefit, but in other controlled experiments the results have not been promising.

It was therefore decided to investigate the action of the antibiotics *in vivo* and *in vitro* from the point of view of their bacteriostatic and bactericidal action. In hospital wards, in particular, the amount of cross infection associated with the presence of the specific types of *Bact. coli* is very great, and there is every need to utilize all available means for its control. No attempt has been made, however, to evaluate the therapeutic action of any of the antibiotics as infantile gastro-enteritis is now, for the most part, a mild disease, and when severe cases do occur adjustment of the water balance gives excellent results.

Methods

The preliminary identification of the specific coliform organisms on plates inoculated with the faeces of infants is difficult because there is no distinctive fermentation reaction. Culture on MacConkey agar, on which, it has been suggested, the organisms have a distinct colonial appearance, is the method preferred, the appearance depending, however, on the composition of the medium. In this laboratory the first examination of the colonies is made by taking a sweep from the plate culture with a platinum loop and emulsifying the material in a drop of 0 K anti-serum diluted 1 in 4 with saline, this method of slide agglutination being effective if the specific organisms are profuse. It is not effective if the specific colonies are greatly outnumbered by other coliforms, and roughness may cause spurious slide agglutination and may be revealed by a control slide test in 1 in 500 acriflavine in saline. If the sweep from the original plate gave a positive slide agglutination test several colonies could usually be identified quickly and picked on to agar tubes for further serological and biochemical tests. If, however, the original sweep was negative then seven individual colonies were inoculated in parallel lines across an agar plate and these subcultures after incubation were examined by slide agglutination.

The biochemical tests on 0111 B4 strains were remarkably constant, and the fact that the H2 variety ferments

TABLE 1

IN VITRO BACTERIOSTATIC ACTION OF ANTIBIOTICS ON *BACT. COLI* ASSOCIATED WITH INFANTILE GASTRO-ENTERITIS

Strains	No. tested	No. of Strains Inhibited after Incubation for 24 Hours at 37°C. in Antibiotic (concentration μg./ml.)						No. of Strains Inhibited after Incubation for 48 Hours at 37°C. in Antibiotics (concentration μg./ml.)					
		50	25	12·5	6·25	3·1	1·5	50	25	12·5	6·25	3·1	1·5
						(1) *Dihydro-streptomycin*							
0111 B4 H2 ..	24	12	6	4	0	0	0	8	6	1	0	0	0
0111 B4 H12 ..	24	15	14	6	2	0	0	10	8	0	0	0	0
055 B5 H6 ..	24	14	11	7	6	1	0	15	7	5	3	0	0
						(2) *Aureomycin hydrochloride*							
0111 B4 H2 ..	24	24	18	18	8	3	0	18	10	6	2	0	0
0111 B4 H12 ..	24	24	24	24	15	6	0	20	12	12	3	0	0
055 B5 H6 ..	24	24	21	21	14	9	0	19	17	10	3	0	0
						(3) *Chloromycetin*							
0111 B4 H2 ..	24	24	24	24	22	2	0	24	24	20	4	2	0
0111 B4 H12 ..	24	24	24	24	6	2	0	24	24	18	3	0	0
055 B5 H6 ..	24	24	24	23	17	9	0	24	24	22	7	0	0
						(4) *Terramycin hydrochloride*							
0111 B4 H2 ..	24	24	24	22	22	6	2	24	24	20	10	6	0
0111 B4 H12 ..	24	24	24	24	18	15	1	24	18	18	18	12	0
055 B5 H6 ..	24	24	24	22	17	10	0	24	24	21	17	8	0

saccharose and that H12 does not was of great value in the preliminary orientation of these sub-varieties. Rare strains of the two serological sub-types also fail to produce gas. The sugar reactions of the 055 B5 strains were also uniform and any deviation made re-investigation of the strains necessary.

The actions of dihydro-streptomycin, aureomycin, chloromycetin, and terramycin on 0111 B4 and 055 B5 were tested in tubes containing 1 ml. of broth and quantities of antibiotic ranging from 50 to 1·5 μg., one drop of a 1 in 10 dilution of a 24-hour broth culture of the strain to be tested being added to each tube. Inhibition of growth was noted after incubating for 24 hours at 37° C. and at the same time a subculture was made from each tube showing no visible growth onto a MacConkey plate to see if there had been any bactericidal effect. The tubes were again incubated for a further period of 24 hours and then re-examined for bacteriostatic and bactericidal effects.

In vitro Sensitivity of Strains to Antibiotics

Twenty-four strains of each of the 0111 B4 H2, 0111 B4 H12 and 055 B5 H6 varieties were tested for sensitivity to the various antibiotics. These strains included nine from the collection of Dr. Joan Taylor; the rest were obtained locally. The bacteriostatic effects of antibiotics are recorded in Table 1 and the bactericidal in Table 2. There was no evidence that any one of the varieties was more sensitive than another to any one antibiotic in regard either to its bacteriostatic or to its bactericidal power. The most inhibitory antibiotic both at 24 hours and at 48 hours was terramycin, followed by chloromycetin, then aureomycin and finally by dihydro-streptomycin. Very few strains were inhibited by 1·5 μg. per ml. and then only by terramycin after incubation for 24 hours but not after 48 hours. Most strains were

TABLE 2

IN VITRO BACTERICIDAL ACTION OF ANTIBIOTICS ON *BACT. COLI* ASSOCIATED WITH INFANTILE GASTRO-ENTERITIS

Strains	No. Tested	No. of Strains Killed after Incubation for 24 Hours at 37°C. in Antibiotic (concentration μg./ml.)						No. of Strains Killed after Incubation for 48 Hours at 37°C. in Antibiotic (concentration μg./ml.)					
		50	25	12·5	6·25	3·1	1·5	50	25	12·5	6·25	3·1	1·5
						(1) *Dihydro-streptomycin*							
0111 B4 H2 ..	24	6	2	0	0	0	0	7	5	0	0	0	0
0111 B4 H12 ..	24	7	4	0	0	0	0	8	3	0	0	0	0
055 B5 H6 ..	24	10	2	2	1	0	0	12	2	2	1	0	0
						(2) *Aureomycin hydrochloride*							
0111 B4 H2 ..	24	0	0	0	0	0	0	2	0	0	0	0	0
0111 B4 H12 ..	24	0	0	0	0	0	0	1	0	0	0	0	0
055 B5 H6 ..	24	0	0	0	0	0	0	2	1	0	0	0	0
						(3) *Chloromycetin*							
0111 B4 H2 ..	24	0	0	0	0	0	0	3	1	0	0	0	0
0111 B4 H12 ..	24	0	0	0	0	0	0	2	1	0	0	0	0
055 B5 H6 ..	24	0	0	0	0	0	0	1	0	0	0	0	0
						(4) *Terramycin hydrochloride*							
0111 B4 H2 ..	24	0	0	0	0	0	0	4	1	0	0	0	0
0111 B4 H12 ..	24	0	0	0	0	0	0	3	1	0	0	0	0
055 B5 H6 ..	24	0	0	0	0	0	0	8	0	0	0	0	0

inhibited by the larger concentrations of all antibiotics except dihydro-streptomycin, in which many strains grew freely even in concentrations of 50 and 25 μg. per ml. As seen in Table 2 aureomycin, chloromycetin and terramycin were not completely bactericidal in any concentration after 24 hours' incubation and killed only a few strains in the higher concentrations after 48 hours. When a drop from each tube was plated on MacConkey medium after incubating for 24 hours the number of colonies growing from the broth containing 50 μg. per ml. of antibiotic was small compared with the number growing from loopfuls taken from the tubes with lower concentrations. On the other hand although dihydro-streptomycin was the least inhibitory it was most bactericidal. It apparently killed about half the strains which were inhibited at 24 hours and about three-quarters of the strains inhibited at 48 hours. Similar results were obtained on 12 strains of *Bact. coli* picked at random from faecal cultures from conditions other than infantile gastro-enteritis.

One strain of anaerogenic 0111 B4 H12 obtained from Dr. Taylor and three strains of anaerogenic 0111 B4 H2 isolated originally from cases in Edinburgh were also tested in the same way and all seemed to be slightly more sensitive to the bacteriostatic action of the drugs than the members of the same serological type producing gas.

In vivo Sensitivity of Strains to Antibiotics

As mentioned previously, it is not proposed to evaluate the effects of antibiotics in the treatment of infantile gastro-enteritis but simply to review the cases to see if these drugs caused the disappearance of the serological types of *Bact. coli* from the faeces. The cases included were those in which only one drug or antibiotic had been employed for treatment throughout the course of the illness.

All the patients were treated in a similar fashion and on admission were starved for 24 hours or longer during which period the milder cases received half strength Ringer lactate solution orally in quantity depending on the weight and based on the formula of 100 ml. per pound per day, while if dehydration was severe the same fluid and same relative quantity was given intravenously by drip, using a polythene cannula. Oral feeding was gradually introduced starting with one-quarter strength milk feeds, increasing through half, three-quarters, to full strength over a period of four days. In the treatment of these cases the first essential is to restore the fluid balance and in severe cases the intravenous infusion of fluid is probably the most important life-saving therapeutic aid available.

Immediately a patient was admitted a specimen of faeces was sent to the laboratory for examination, and if this showed a specific serological variety of *Bact. coli* and if the case was not to be used as a control, then the appropriate drug was given as follows:

Sulphamezathine	0·5 g. to begin with followed by 0·25 g. every four hours orally
Penicillin	50,000 units to begin with followed by 25,000 four-hourly parenterally
Polymyxin	50 mg. in six-hourly doses orally
Dihydro-streptomycin	20 mg. per kg. in six-hourly doses parenterally
Aureomycin hydrochloride	10 mg. per kg. in six-hourly doses orally
Chloromycetin	50 mg. per kg. in six-hourly doses orally
Terramycin hydrochloride	50 mg. per kg. in six-hourly doses orally

The courses of treatment lasted six days in all, and thereafter a specimen of faeces was sent for bacteriological examination while further specimens were sent twice weekly until the patient was discharged from hospital. If, however, the faeces were still positive, then a second course of treatment was instituted, and if necessary a third.

It is customary to divide cases of gastro-enteritis into varying degrees of severity, mild, moderate and severe, but as the severity of the disease has greatly diminished they have been classified as mild and severe. Those with no symptoms of illness and yet showing the specific *Bact. coli* varieties in the faeces have been designated carriers. Comparatively few cases infected with the 0111 B4 H2 variety have been treated, due to the virtual disappearance of this organism, while cases infected with the new type 026 B6 have only been encountered nine times and the only organism prevalent has been the 055 B5 with the H6 antigen.

Table 3 shows the results in the cases infected with the 0111 B4 H2 strains. The cases treated with each drug, however, were so few that no definite conclusion could be drawn except to say that the organisms disappeared from the faeces in the control cases in about the same time as they disappeared from those of the treated ones.

There were 140 cases infected with the 055 B5 H6 strains, 102 clinical cases and 38 carriers, the particulars of this group being given in Table 4. In the investigation of the duration of infectivity the period of illness before admission has not been taken into account, and it has been assumed that the specific coliform organisms are unlikely to remain longer in the intestine of the clinical case than in the intestine of the temporary carrier. As the course of treatment lasted six days and as a further two days were allowed for the flora of the intestine to resume some semblance of normality, the minimum period in which a case could become negative was eight days. In the control series of cases the average duration

TABLE 3
DISAPPEARANCE OF *BACT. COLI* 0111 B4 FROM CASES OF GASTRO-ENTERITIS AND CARRIERS

	Type of Case							
	Mild		Severe		Carriers		All	
	No. in Series	Days Infective	No. in Series	Days Infective	No. in Series	Days Infective	No. in Series	Days Infective
Controls	12	9	3	12	3	9	18	9
Sulphamezathine	2	7	–	–	1	6	3	7
Polymyxin	6	9	–	–	–	–	6	9
Aureomycin hydrochloride	2	12	–	–	–	–	2	12
Totals	22		3		4		29	

of infectivity after admission was 16 days. There appeared to be a slight reduction in this period after the administration of sulphamezathine and streptomycin, but none after penicillin, and only a slight reduction after polymyxin. Aureomycin was only used in a few cases but chloromycetin and terramycin showed little evidence of being any more effective. These results do not mean that the effect of giving an antibiotic or suppressive drug was negligible, for while the patient was under treatment the coliform flora of the intestine could frequently no longer be cultured on MacConkey plates and the organisms obtained, if any, belonged to the *Proteus* group. This inhibition must therefore limit the spread of cross infection.

The Effect of Terramycin on the Faecal Flora of Children in an Institution

On June 25, 1951, an outbreak of gastro-enteritis occurred in Thorngrove Home, a residential nursery where there were 21 infants whose ages ranged from 1½ to 10 months. Three moderately severe clinical cases were admitted to the gastro-enteritis unit at the City Hospital, and among the 18, housed in two rooms at Thorngrove Home, seven developed loose stools and loss of weight—mild symptoms of gastro-enteritis. The faeces from all cases were then examined for agglutinable *Bact. coli* and it was found that the specimens from three cases admitted to the City Hospital, from seven mild cases and from five children without clinical symptoms in Thorngrove Home, all showed the 055 B5 H6 type of *Bact. coli* (Table 5). Under these circumstances it was not thought advisable to admit any more cases to hospital but simply to treat all 18 cases (12 infected and six non-infected) remaining in Thorngrove Home with terramycin to see what would happen to the specific type of *Bact. coli*. Accordingly each child was given 100 mg. of terramycin in the elixir form by mouth four times daily for six days. Two days later, in order to give time for the disappearance of some of the effects of the antibiotics, the faeces were again examined. The flora of nine of the specimens consisted mainly of organisms belonging to the *Proteus* group, but the other nine were fairly normal so far as coliforms were concerned, and one of these showed the 055 B5 H6 type again. No further treatment was administered and the faeces were examined eight days later. This time the coliform flora in all specimens were normal and seven of the previously positive cases again showed the 055 B5 H6 type in the faeces. A further course of terramycin was given to each of the seven positive cases and two days after its termination all specimens from previous positive and negative cases alike were examined. This time four specimens from cases positive at the previous examination were still positive and in addition the faeces of three of the

TABLE 4
DISAPPEARANCE OF *BACT. COLI* 055 B5 H6 FROM THE FAECES OF CASES OF GASTRO-ENTERITIS AND CARRIERS

Treatment	Type of Case							
	Mild		Severe		Carriers		All	
	No. in Series	Days Infective	No. in Series	Days Infective	No. in Series	Days Infective	No. in Series	Days Infective
Control	20	18	6	14	7	12	33	16
Sulphamezathine	5	12	3	14	1	13	9	13
Penicillin	5	19	3	20	–	–	8	19
Polymyxin	10	9	6	15	1	25	17	12
Dihydro-streptomycin ..	7	13	4	20	4	19	15	16
Aureomycin hydrochloride	2	18	1	12	4	10	7	12
Chloromycetin	13	17	8	13	14	12	35	14
Terramycin hydrochloride	8	14	1	8	7	20	16	16
Total	70		32		38		140	

TABLE 5

PLATE CULTURES ON MacCONKEY MEDIUM FROM 18 PATIENTS FROM THORNGROVE HOME TESTED BY 'SWEEP' AND COLONY SLIDE AGGLUTINATION TESTS USING 055 B5 0B ANTISERUM

Examination	Date	'Sweep Test'* (degree of agglutination)				Colony Agglutination Test† (seven tested from each plate)								Acriflavine Control Tests
		+++	++	+	−	7	6	5	4	3	2	1	0	
First after outbreak	25.6.51	10	2	1	5	10	0	0	0	1	1	0	6	Colonies on one plate rough
Terramycin to all														
Second	2.7.51	0	0	1	17	0	0	0	0	0	0	1	17	Colonies on one plate rough
Third	10.7.51	4	1	1	12	0	3	0	0	0	3	1	11	No rough colonies on plates
Terramycin to all previous positives														
Fourth	17.7.51	6	1	1	10	3	2	1	0	0	0	1	11	Colonies on two plates rough
Terramycin to all previous positives														
Fifth	31.7.51	1	1	3	13	1	0	0	0	0	1	0	16	Colonies on three plates rough
Sixth	9.8.51	1	1	0	16	1	0	0	0	0	1	0	16	No rough colonies on plates

* Plate cultures giving slide agglutinations. † Colonies giving positive slide agglutinations.

originally infected children were again positive. A fourth course of terramycin was then given to all positive cases, and after this was completed specimens on two occasions from all 18 children showed only two individuals still carrying the organisms. These two children were then transferred to the gastro-enteritis unit at the City Hospital for isolation where a further course of treatment eliminated the specific type. All the children throve well while taking terramycin, and despite the uncertainty as to its effect from the therapeutic aspect there is no doubt that the giving of the drug inhibited the growth of the organisms, thereby reducing the chances of cross-infection.

Also in Table 5 are tabulated the findings after seven colonies of *Bact. coli* from a MacConkey plate from each faecal specimen had been examined serologically. To begin with the specimens from 10 out of 12 positive cases (seven clinical cases and three carriers) showed apparently pure cultures of the 055 B5 H6 type, while the specimens from two carriers showed three and two colonies out of the seven examined. Later, after further treatment with terramycin, the clinical cases still gave the higher proportion of positive colonies and at the end of the period of observation one was still showing a pure culture. Finally, none of the six negative cases at the first examination later became positive.

Discussion

The degree of the bacteriostatic or bactericidal action of an antibiotic *in vitro* is determined by such factors as the number of organisms employed, the age of the culture, the composition and hydrogen ion concentration of the culture medium, the temperature and duration of exposure during incubation, and the concentration of the antibiotic. Furthermore these factors can probably be made less variable under experimental conditions in the laboratory than in an *in vivo* test, when, for example, the inhibition or clearance of certain types of *Bact. coli* from the intestines of animals or man is attempted.

The *in vitro* experiments demonstrate that, though the strains of *Bact. coli* are frequently markedly inhibited by low concentrations of antibiotics for the first 24 hours of incubation at 37° C., this action is not convincingly maintained up to periods of 48 hours except where the concentration of antibiotic amounts to 25 or 50 μg. per ml. Furthermore, the bactericidal action is less marked than the bacteriostatic, and dihydro-streptomycin, which was the least effective in its inhibitory action, was most effective in its germicidal capacity. The difference between the concentration of antibiotic necessary to produce bacteriostasis and a germicidal action is less with this substance than with the other antibiotics if the organism is sensitive. It is possible that during incubation *in vitro* at 37° C. for more than a short period there is a considerable deterioration in the small amount of antibiotic contained in the culture fluid. Experiments by Bryson and Demerec (1950) have shown, however, that when terramycin is diluted in broth and incubated at 37° C. there is a slight deterioration in its inhibitory effect after 48 hours, still more after 72 hours, while at 96 hours it is almost ineffective.

Though the tests on children have not been

satisfactory from the point of view of clearing the intestines rapidly of specific types of *Bact. coli* this may to some extent be due either to inadequate dosage or to too short a period of treatment. The faeces in the control cases, both clinical and carrier, became negative almost as soon as in those treated with an antibiotic. An infectivity period of 16 days after admission seems to be about the average for this type of infection, though some treated cases have been found to remain positive for over three weeks and certain carriers for as long as five. One fact, however, is manifest and that is, while a child is undergoing treatment with aureomycin, chloromycetin, or terramycin, the *Bact. coli* flora and particularly the specific types under investigation are very markedly suppressed and this in itself is bound to limit the possible spread of cross infection. Administration of the drugs for a longer period might produce additional advantageous results. In the test trial of terramycin on children in an institution the dosage given was less than in the gastro-enteritis unit and the period over which it was administered was considerably extended by waiting for complete bacteriological results to become available.

Drug resistance has not been studied but the work of others has shown that coliform organisms may develop resistance to streptomycin very rapidly, whereas with aureomycin, chloromycetin and terramycin resistance develops much more slowly. No ill effects have been noted following the elimination of the coliform flora from the intestines and the establishment of members of the *Proteus* group, and the withdrawal of the antibiotic soon permits the coliform organisms to predominate again. In addition the infants treated with antibiotics have shown no complicating side effects such as involvement of the mucous membrane of the mouth, tongue, anus and vagina. Following on terramycin therapy, in particular, the weight of an infant seems to increase at a slightly greater rate than in an untreated child.

At the best, therefore, the newer antibiotics now in use cannot be expected to do more than produce bacteriostasis in the intestine of members of the *Bact. coli* group. The high concentration necessary for bactericidal action can be obtained only in the test tube and is unlikely to be obtained, after oral administration, in the gastro-intestinal tract. Further effectiveness of the bacteriostatic action in the bowel is probably influenced by many factors connected with the composition of its contents.

Summary

Tests have been carried out *in vitro* and *in vivo* on the effect of antibiotics on the specific types of *Bact. coli* associated with infantile gastro-enteritis.

The *in vitro* tests showed that low concentrations of aureomycin, chloromycetin and terramycin had a marked inhibitory action on growth over a period of 24 hours at 37° C. and very much less at 48 hours. Dihydro-streptomycin was less effective.

The bactericidal action of aureomycin, chloromycetin and terramycin was relatively weak and was only evident in high concentrations of 25 and 50 μg. per ml. and then only on the more susceptible strains. Dihydro-streptomycin, in the higher concentrations, had a bactericidal action on a greater number of strains.

The *in vivo* tests with the antibiotics have shown that suppression of the coliform flora of the intestine could be effectively obtained, these organisms being largely replaced by members of the *Proteus* group.

So long as oral administration was continued the specific types of *Bact. coli* were held in check but with the cessation of treatment they tended to re-appear.

Antibiotic therapy did not appear to lessen the total period of infectivity with the specific coliform types, though presumably while being employed it limited the possibility of cross-infection simply by reducing the number of organisms excreted.

Owing to the present mildness of infantile gastro-enteritis no attempt has been made to evaluate the therapeutic action of the antibiotics studied.

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KILLED ANTI-TUBERCULOSIS VACCINE AND HYALURONIDASE (DIFFUSING VACCINE)

BY

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Hyaluronidase was first used in human anti-tuberculosis vaccination in 1950 (Salvioli, 1933).

From the very first it was possible to see that the addition of hyaluronidase increases remarkably the vaccinating activity of killed tubercle bacilli injected intradermally. Also it was confirmed that their diffusion offered an interesting field of study not only of vaccinating antigens consisting of microbic bodies or of organized structures, but also of extractive antigens, of immune sera and of antibiotic drugs (Salvioli, 1933).

The hypothesis that led to the use of a vaccine associated with hyaluronidase, termed diffusing vaccine (V.D.S.*), in anti-tuberculosis vaccination, was the same that about 20 years ago led me to perform intradermal vaccinations with *Anatubercolina I. petragnani*, using a plurifocal method (V.D.S.). The aim of this latter method is to produce a vast tissue process with an adequate dose of vaccine.

Anti-tuberculosis vaccination with killed bacilli with the addition of diffusing vaccine aims at vaccinating and protecting the organism by using only one injection of a reduced amount of vaccine. The focus of injection often appears less prominent than with the use of germs without hyaluronidase; it is more extensive, showing that the region of tissue involved in the constitution of the vaccinial focus is greater. As I pointed out many years ago, the vaccinial focus is the essential factor for the creation of resistance against virulent tubercle bacilli produced by a vaccine.

Killed tubercle bacilli have been used in V.D.S. vaccination tests for two years. Their vaccinating and protective properties were widely shown in practice in newborn children (Salvioli, 1951a and b) as well as in various experiments in guinea-pigs and dogs.

In man V.D.S. vaccination has been predominantly employed in infants, but some older individuals who had no allergy have also been injected. The vaccine was inoculated intradermally into the palmar surface of the forearm and caused no general disturbances. The vaccinial focus had a slower and much longer evolution than that following vaccination without the addition of hyaluronidase. As soon as allergy has developed there is a phenomenon of recidivation which may lead to the formation of small superficial eschars and moderate secretion, especially in older individuals. The scar is mostly smooth or linear, and may even be absent.

Allergy appears after three or four months (Fig. 1).

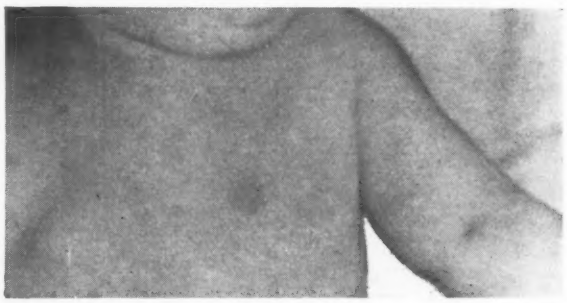

FIG. 1.—Vaccinial focus on the forearm five months after vaccination; positive plaster-reaction on the chest.

In some subjects in whom the vaccinial process is very slow allergy may appear as late as six months after vaccination, but this is an exceptional occurrence. The percentage of allergy after one year is about 95. These results were obtained with relatively moderate doses compared with other vaccination methods; the doses were further reduced according to the age of the patient.

An explanation of the better action of vaccine associated with hyaluronidase is provided by studies made on rabbits in the Anti-tuberculosis Vaccinio-prophylactic Centre of Bologna (Salvioli, Degli Esposti and Dina, 1952a and b). Histochemical tissue reactions produced by vaccines of heat-killed tubercle bacilli with the addition of hyaluronidase were studied in comparison with those caused by the vaccine alone. It was found that the diffusion of killed tubercle bacilli causes a much greater inoculation focus in the skin than with tubercle bacilli

* Known in Italy as V.D.S. (*vaccino diffondente Salvioli*).

alone; this focus shows slower development and less probability of eliminating the inoculated bacterial bodies.

Histochemically the results obtained with V.D.S. are the following. In the vaccination focus the typical specific tissue with granulomas of epitheloid giant cells and necrobiotic aspects are found. In the satellite (crural) lymph nodes there is in 60% of the cases a typical tuberculous reaction similar to that in the vaccinial focus. In the inguinal satellite nodes at the vaccinial focus tuberculous granulomas are always present together with a remarkable increase of the light-coloured centres, with numerous plasma cells, Russell's hyaline bodies and a diffuse proliferative histiocytic reaction. In the lymph nodes contralateral to the vaccinial focus the picture is very similar to the preceding one.

In the spleen an increased number of follicles and the formation of germinal centres are observed; in the pulp a proliferative hystiocytic reaction and numerous small foci showing haemopoietic activity are seen. Hyperaemia is marked and in the sinuses some large endothelial cells with phagocytic properties are present.

A swelling of Kupffer's cells is always present in the liver and sometimes, though more rarely, signs of mobilization.

The histochemical features encountered in individuals vaccinated with killed germs alone, except for the constant absence of specific lesions in the satellite lymph nodes at the vaccinial focus, are of the same type as those seen in rabbits vaccinated with V.D.S., but of lesser degree and constancy, especially in the findings of the spleen and liver. Pyroninophilia is much intenser in V.D.S.-vaccinated individuals, especially near the vaccination focus. Sivori's enzyme reaction gives almost double values in V.D.S. vaccination subjects, in comparison with those obtained by simple vaccination.

All these facts show that the diffusing factor produces in the killed germs that migratory property characteristic of living germs, thus determining a 'vaccination complex' analogous to Ranke's primary complex which is known to modify the reaction of the organism to subsequent contacts with tubercle bacilli.

The specific lesions of the satellite lymph nodes during diffusing vaccination represent a direct stimulus for a tissue containing many mesenchymal elements, thus greatly increasing the specific involvement of the reticulo-endothelial system.

The original type of diffusing vaccination with killed germs, therefore, produces the same characteristics as those obtained with living germs without, however, having their disadvantages.

The foregoing facts allow us to speculate on the mechanism of anti-tuberculosis and other vaccination, and on the constitution of various immunization phenomena, light on which may be obtained through a controlled use of the diffusing factor.

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OBSERVATIONS ON FOETAL HAEMOGLOBIN

BY

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Foetal haemoglobin exhibits a much greater resistance towards alkaline denaturation than does adult haemoglobin, thus constituting an important distinction between the two types of haemoglobin. The phenomenon was first described by Körber (1866), observed again by Krüger (1887-88), and subsequently studied in more detail by Bischoff (1926), Haurowitz (1929, 1930), and Brinkman, Wildschut and Wittermans (1934). The latter developed a photoelectric method that enabled them to work with mixtures of pigments having different degrees of resistance to alkaline denaturation.

Further study has demonstrated that the two types of haemoglobin differ also in many other properties (Table 1). However, the most pronounced difference so far described is to be noted in the speeds of denaturation by alkali, but the mechanism is not yet understood. No report could be found in the literature describing the behaviour of the two types of haemoglobin under the influence of other denaturing agents.

Among such agents, urea and salicylates are known to bring about denaturation of haemoglobin, and at the same time maintain the thus denatured protein in solution. Urea in concentrated solution causes denaturation of haemoglobin and, in addition, horse (Astbury and Lomax, 1935) or ox (Huang and Wu, 1930) haemoglobin molecules are dissociated into half molecules as determined by osmotic pressure measurements. The effect of varying concentrations of urea and related amides on horse haemoglobin has been studied extensively by Steinhardt (1938) who found, when working with horse methaemoglobin formed by the action of potassium ferricyanide, that within 20 hours at room temperature the characteristic absorption spectral band in the red (630μ) fades and is replaced by a diffuse band in the green (at approximately 534μ). It was concluded that the latter band was not due to ferrohaemochromogen since, on treatment with sodium hydrosulphite, the typical absorption spectrum of ferrohaemochromogen did not appear.

The denaturing effect of sodium salicylate on bovine methaemoglobin was examined in detail by Anson and Mirsky (1934). They measured the increase in the spectral absorption in the green and found that when salicylate was added to native methaemoglobin the absorption in the green at first increased rapidly, then remained constant and finally increased again very slowly. The concentration of salicylate in their experiments varied from 0·05 M to 0·5 M and they observed that greater proportions of denatured protein were produced and with increasing concentration of salicylate the speed of reaction was also increased. Using 0·5 M salicylate solutions denaturation was complete in 30 minutes.

In the present study we have subjected foetal and adult methaemoglobin to the denaturing action of urea and salicylate and studied the behaviour of the two pigments. These two denaturing agents were chosen since, in the concentrations used, they possess the property of keeping the denatured protein in solution, thus facilitating spectroscopic studies and photometric determinations.

Experimental

Material. Venous blood freshly withdrawn from healthy adults and cord blood were used as sources of adult and foetal haemoglobin respectively; cord blood contained foetal haemoglobin in concentrations varying from 75% to 85% of the total haemoglobin as determined by the technique of Ponder and Levine (1949).

Pure haemoglobin solutions were prepared from the erythrocytes after repeated washings with 0·9% w/v NaCl; dilution with 1·0 to 1·5 vol. of distilled water, thorough mixing with 0·4 vol. toluol, centrifugation, and siphoning off the clear haemoglobin solution which was finally filtered.

Methaemoglobin was prepared from the above haemoglobin solutions by the use of potassium ferricyanide according to Anson and Mirsky (1931). The reaction is stoichiometric and 1·1 mol. of the oxidizing agent was added per atom of Fe using 1% w/v solution of $K_3Fe(CN)_6$.

An 8·8 M urea solution and a 1·0 M sodium salicylate solution (both 'analar') were prepared, the latter being filtered and stored in the cold as suggested by Anson and Mirsky (1934).

TABLE 1

SUMMARY OF DIFFERENCES BETWEEN FOETAL AND ADULT HAEMOGLOBINS

Phenomenon	Distinctive Property	Reference
Alkaline denaturation ..	Foetal haemoglobin more resistant than adult	Körber (1866) Krüger (1887) Bischoff (1926) Haurowitz (1929-30) Brinkman *et al.* (1934)
O_2 dissociation curve ..	Foetal haemoglobin inside the erythrocyte has a higher oxygen affinity and smaller value of 'n' in the Hill equation than adult haemoglobin.	Haurowitz (1935) McCarthy and Popják (1943)
Solubility behaviour ..	Definite difference in the solubility curves between human adult and foetal haemoglobin CO, haemoglobin O_2 and methaemoglobin. In strong phosphate buffer foetal haemoglobin is more than six times as soluble as adult haemoglobin.	Jope and O'Brien (1949) Wyman, Rafferty and Ingalls (1944)
Crystallographic data ..	Different characteristics in crystalline forms.	Jope and O'Brien (1949)
Spectroscopic differences ..	In human foetal haemoglobin the fine 'tryptophane absorption band' appears at 289·8μ and in adult haemoglobin at 291·0μ.	Jope (1949)
Amino-acid composition ..	Human foetal haemoglobin contains 2·6 terminal valyl residues per molecule compared with 5 in human adult haemoglobin. Bovine adult haemoglobin contains more histidine than foetal haemoglobin.	Porter and Sanger (1948) Vickery (1942)
Peroxidative effect ..	Human foetal haemoglobin exhibits greater peroxidative activity than adult haemoglobin.	Betke (1950)

Methods. Before its conversion to methaemoglobin the haemoglobin concentration was determined in an E.E.L. photoelectric colorimeter. The changes in the absorption during the experiment following the addition of the denaturing agent were determined using a 'unicam' diffraction grating spectrophotometer, and a Hartridge reversion spectroscope was employed for the spectroscopic observations.

Urea. Steinhardt's experimental conditions were applied. All solutions contained 0·14 g. methaemoglobin per 100 ml. and 0·1 M KCl. The concentration of urea was 4·4 M while the control solutions contained an equal volume of distilled water. The final volume of each solution was 10 ml. The optical density was measured at 630μ and 540μ, taking readings every two hours for 24 hours.

RESULTS. The results obtained expressed as the mean of several experiments are summarized in Table 2. It shows that the rate of denaturation of foetal methaemoglobin was quicker than that of adult methaemoglobin. Each individual experiment followed a very similar pattern and in no instance was the reading with the solution of foetal methaemoglobin at 540μ lower than with the adult. At eight hours the denaturation of foetal methaemoglobin reached a stage which adult methaemoglobin attained only after 24 hours. The contrast in colour between the two solutions was apparent even to the naked eye.

Addition of sodium hydrosulphite produced the typical ferrohaemochromogen spectrum in both foetal and adult methaemoglobin solutions contrary to Steinhardt's observations. There was, however, a marked time difference, typical ferrohaemochromogen appearing at eight hours in the foetal methaemoglobin solution and at 24 hours in the adult methaemoglobin solution.

Salicylate. Anson and Mirsky's (1934) experimental conditions were applied. All solutions contained 0·1 g. methaemoglobin per 100 ml. in 0·1 M phosphate buffer, *p*H 6·8. Varying volumes of 1·0 M sodium salicylate solution were added to obtain solutions containing 0·0, 0·2, 0·4, 0·5 M salicylate. The final volume of each solution was 10 ml. Readings were obtained at 540μ before and at 0·5, 3, 5, 10, 15, 30, 60 and 120 minutes after the addition of salicylate.

RESULTS. Table 3 summarizes the results obtained and presents the mean of several experiments. This shows in contrast that the speed of denaturation of foetal methaemoglobin by salicylate was slower than that of the adult pigment in all concentrations. Each individual experiment led to the same conclusion and in no instance were the results conflicting. For the fuller appreciation of this fact from the table it must be noted that a difference of, say, 0·03 in the optical density represents over 10% of the total denaturation.

When sodium hyposulphite was added at 60 minutes, the typical ferrohaemochromogen spectrum was obtained in all solutions with salicylate.

Discussion

The above experiments show that foetal and adult haemoglobins, besides differing in stability to alkaline denaturation as already known, differ also in their resistances to denaturation by urea or sodium salicylate. The fact that the two types of blood pigment behave differently according to the denaturing agent, viz. higher resistance of foetal haemoglobin to denaturation by alkali or salicylate and lower resistance towards urea, can be understood in the light of the modern concept that denaturation is not a single phenomenon; that there

TABLE 2

RATE OF DENATURATION OF ADULT AND FOETAL METHAEMOGLOBIN BY 4·4 M UREA AS DETERMINED BY THE INCREASE IN SPECTRAL ABSORPTION AT 540μ*

Time (minutes)	Adult Methaemoglobin				Foetal Methaemoglobin			
	Solution 1 (with Urea)		Solution 2 (Control)		Solution 3 (with Urea)		Solution 4 (Control)	
	630μ	540μ	630μ	540μ	630μ	540μ	630μ	540μ
0	0·54	0·82	0·49	0·75	0·54	0·84	0·49	0·74
2	0·53	0·86	0·49	0·765	0·50	0·93	0·50	0·745
4	0·51	0·89	0·49	0·765	0·45	0·98	0·50	0·745
6	0·50	0·90	0·49	0·76	0·43	0·99	0·50	0·755
8	0·50	0·91	0·51	0·765	0·42	1·00	0·51	0·76
12	0·49	0·92	0·49	0·76	0·40	1·04	0·50	0·76
14	0·49	0·92	0·49	0·76	0·39	1·05	0·49	0·75
16	0·50	0·94	0·48	0·76	0·37	1·06	0·48	0·76
18	0·48	0·95	0·48	0·765	0·37	1·07	0·50	0·77
20	0·44	0·98	0·49	0·765	0·32	1·07	0·49	0·75
24	0·42	1·00	0·48	0·765	0·30	1·09	0·48	0·75

All solutions contained 0·14 g. methaemoglobin per 100 ml. and 0·1 M KCl. Final volume of each solution = 10 ml.
* Readings express optical density and present the mean of several experiments.

are various kinds of denaturation; and that in each one of them the changes may involve various groups of the protein molecule.

The differences between the two types of haemoglobin described in the present paper in addition to those already described (Table 1) leave little doubt that there are definite ontogenetic variations of haemoglobin. Since the prosthetic haemin is identical in various haemoglobins the distinction between the two types must be attributed to the protein moieties. It is now accepted that the globin components of foetal and adult haemoglobin are different. In favour of this view further evidence has recently been brought forward by Betke (1950), who found that while haemin prepared from adult and foetal haemoglobin had similar peroxidative activity, foetal haemoprotein exhibited higher peroxidative activity than adult.

It would appear reasonable to subscribe to Drabkin's (1951) hypothesis that a structurally identical haemin combines with the particular and suitable protein available at the site of chromoprotein fabrication; thus 'liver' globin may be held responsible for the properties of foetal haemoglobin, and 'red bone marrow' globin for those of adult haemoglobin. However, this latter observation requires further experimental study.

Summary

A definite contrast in the speed of denaturation between foetal and adult haemoglobins was observed when urea and sodium salicylate were the denaturing agents.

In 4·4 M urea solution foetal methaemoglobin denatured more quickly than adult methaemoglobin.

In solutions of sodium salicylate (0·2 to 0·5 M) foetal methaemoglobin was more resistant than adult methaemoglobin to denaturation.

The problem of differences of the two types of blood pigment is considered.

TABLE 3

RATE OF DENATURATION OF ADULT AND FOETAL METHAEMOGLOBIN BY SALICYLATE AS DETERMINED BY THE INCREASE IN SPECTRAL ABSORPTION AT 540μ*.

Time (minutes)	Control		Salicylate Concentration					
			0·2 M		0·4 M		0·5 M	
	A.	F.	A.	F.	A.	F.	A.	F.
0·5	0·41	0·41	0·50	0·47	0·61	0·59	0·66	0·62
3			0·535	0·495	0·66	0·62	0·665	0·63
5	0·41	0·41	0·55	0·50	0·66	0·625	0·665	0·63
10			0·56	0·51	0·66	0·625	0·665	0·63
15	0·415	0·415	0·56	0·52				
30			0·56	0·53	0·66	0·63	0·67	0·63
60	0·415	0·415	0·57	0·54				
120	0·415	0·415	0·575	0·56	0·67	0·635	0·68	0·64

A. = Adult. F. = Foetal.
* Readings express optical density.

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A CASE OF TENSION PNEUMOTHORAX COMPLICATING STAPHYLOCOCCAL PNEUMONIA AND EMPYEMA THORACIS

BY

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Empyema thoracis is seldom a primary condition. It must necessarily be considered against the background of infection of the respiratory tract. Staphylococcal pneumonia along with its major complication, empyema, has been recognized as a separate clinical entity for some years, although Agnes Macgregor as recently as 1936 described 10 cases in support of this conception. The extensive use of sulphonamides in the treatment of respiratory infections succeeded in throwing into relief cases unresponsive to these drugs. Not only has there been a relative increase in the incidence of staphylococcal pneumonia but several authors, including Guthrie and Montgomery (1947), have shown that the increase is also a real one.

Secondary staphylococcal pneumonia is distinguished from the primary type by being a complication of a staphylococcal focus of infection elsewhere in the body, for example, osteomyelitis. For the aetiology, clinical features, mortality, etc., in relation to treatment reference may be made to papers by Gibson and Belcher (1951), Guthrie and Montgomery (1947), Kanof, Kramer and Carnes (1939), Dickie (1938) and Chickering and Park (1919).

Two features of staphylococcal pneumonia stand out clearly. First, all accounts of the disease stress the frequency of empyema. Kanof *et al.* (1939) look upon empyema as an integral part of the disease rather than as a complication. In their review of 15 primary and 12 secondary cases 87% of the primary and 58% of the secondary types developed empyemata. Secondly, a strong predilection for the youngest age group is shown, especially by the primary pneumonia. Kanof *et al.* (1939) discussed 23 cases of primary and 12 cases of secondary staphylococcal pneumonia. In the primary cases 70% were under 1 year old, 9% were over 5 years. In the secondary cases, 41% were under 1 year and 25% were over 5 years. The patients were older in the series of secondary pneumonias.

The high incidence of empyema may be related to the extreme youth of the patients. Cohen (1938) suggested that the pleura easily became infected since the layer of lung tissue was very thin. It is generally considered, however, that in many cases the empyema is caused by the rupture of an abscess in the lung into the pleural space. Macgregor (1936) supported this view from the post-mortem findings in 10 fatal cases. She pointed out that the inflammatory process in the lung may be confined to a small area while the whole pleura is often full of pus. Blumenthal and Neuhof (1946) described a 3-year-old girl who had a tension pneumothorax. Stab thoracotomy was performed to relieve respiratory and circulatory distress. Next day there was a sudden expulsion of a muco-purulent plug from the drainage tube, followed by a gush of air lasting some minutes. The authors considered that this event indicated the sudden rupture of another abscess into the pleura. They found in another patient, a 6-year-old boy, a narrow extension of an empyema leading directly to a small collection of pus within necrotic lung.

Since abscesses can discharge spontaneously into the bronchi, it is reasonable to expect that they can burst into the pleural space. The frequent incidence of pyopneumothorax favours this conception. Since, however, localized empyemata also occur not all cases take place in this way. Protective adhesions may have time to form and invasion of the pleura be more gradual. The virulence of the organism, the resistance of the patient, and the efficacy of treatment must influence the incidence and size of an empyema.

The presence of air in the pleural space following or during the course of staphylococcal pneumonia

means the occurrence at some stage of a bronchopleural fistula. It is only possible, in reviewing the literature, to arrive at an approximate idea of the frequency of empyema and pyopneumothorax complicating pneumonia. The main reason for this is the varying virulence of the organism, different methods of treatment (especially of empyema) and the evolution of new chemotherapeutic drugs. Some of the bigger series of cases are analysed here with special reference to pyopneumothorax.

Macgregor (1936) in her series of six non-fulminating but fatal cases out of a total of 10 patients with primary staphylococcal pneumonia reported empyema occurring in 100%. Air was also present in three, and in each of these a bronchopleural fistula was identified at necropsy.

In the description of 23 cases of primary staphylococcal pneumonia and 12 of secondary pneumonias, Kanof *et al.* (1939) had only two cases of pneumothorax occurring before chest aspiration had been attempted; one in a baby girl of 7 months who died, and the other in a girl of 30 months who recovered. No case of tension pneumothorax occurred.

Hochberg and Kramer (1939) found one case of bronchopleural fistula out of 33 cases of staphylococcal empyema. The mortality in the whole series was 22%. Their conclusions were that mortality was proportional to the inadequacy of drainage of the empyema. They were not of the opinion that rupture of pulmonary abscess was the direct cause of an empyema. Under 2 years of age complications associated with empyema were more frequent than above that age.

Clemens and Weens (1942) described six cases of primary staphylococcal pneumonia. Every patient acquired an empyema. Four had pyopneumothorax. All died from toxaemia.

Riley (1944), reviewing 29 cases of empyema caused by staphylococci, made the observation that 76% occurred in the first year and 40% in the first six months. Of 22 infants under 1 year of age, eight died. Of seven over 1 year, two died. No mention is made of pneumothorax or pyopneumothorax in his review.

Ladd and Swan (1943) made an important contribution to the subject in their study of 33 cases of empyema. Twenty-one were under 1 year and 12 were under 4 months. The most important factor influencing the mortality seemed to be the age of the patient. Of 12 patients less than 4 months old, eight died (67%). Of 21 patients over 4 months old, only one died (5%). One case described was that of a 2½-year-old boy who recovered after fulminating laryngo-tracheobronchitis requiring tracheotomy and bronchoscopy. He had bilateral empyema and bilateral tension pneumothorax in addition to underlying pulmonary abscesses. The treatment of their cases was chiefly by drainage and sulphonamides.

Blumenthal and Neuhof (1946) carefully analysed a series of 40 cases of primary staphylococcal pneumonia. Eight were fulminating cases allowing no time before death for the development of advanced pulmonary or pleural changes. A second group of 11 were less overwhelming in their course. Each patient had an empyema in which the whole of one pleural space was affected. The range in age was from 1 month to 3 years. Seven patients died. Five had pus alone in the pleura; three of these died. Six had pyopneumothorax from which four died. In two of these there was tension and a mediastinal shift. Eight of the total of 11 were described as having a bronchopleural fistula.

A third group of 17 were cases in which encapsulated abscesses or empyemata had developed. Fourteen of these were cases with empyema. Their range of age was 1 month to 12½ years, the average age being almost twice that of the previous group. Twelve had pus only, while two had pyopneumothorax. No case of tension pneumothorax was described. Altogether 13 out of the 17 cases had bronchopleural fistula verified by operation for drainage or by radiography using lipiodol instilled via the empyema track. There was no mortality in this group.

Lastly a fourth group was described of four chronic and subacute cases. Each of the four had an empyema. The ages were 7, 7, 2 and 6 years respectively. Three of the four had a bronchopleural fistula, but there was no case of pneumothorax in this small group.

Altogether the mortality in the 40 cases was 15 (or 35%). Eight of the 15 did not acquire empyemata for reasons already stated. Four had pyopneumothorax and three simple empyema (not encapsulated). The numbers are too small for many conclusions to be drawn. They do, however, show that the most serious cases are those in which the whole pleura is flooded with pus, and that when this occurs bronchopleural fistula is probably present and there is a likelihood of air also escaping into the pleura. The presence of air is not in itself an indication that the chance of survival is less. It seems rather that the important feature is the total filling of the pleural space.

Davis, Hyman and Ruhstaller (1947) reported seven cases of primary staphylococcal pneumonia in patients whose ages ranged from 18 days to 11 years. All were complicated by pneumonia. No case of pyopneumothorax was described. One infant aged 2 months died.

Gibson and Belcher (1951) stated that in their experience empyema occurs in 10% to 30% of adults suffering from primary staphylococcal pneumonia and 50% of children. In 10 cases of pneumonia there were four of empyema, one of which was a pyopneumothorax. No patient was under 14 years of age and all recovered. They considered pyopneumothorax to be relatively common in children and that it was a major factor causing death, prognosis being little affected by any form of treatment. Tension pneumothorax, they pointed out, is sometimes difficult to distinguish from a large pulmonary tension cyst, but they did not consider the differentiation of any great moment so far as treatment was concerned. They supported the 'check-valve' conception of air entering the pleura on inspiration but being unable to escape during expiration in the same manner that large cysts in the lung may develop.

The chief danger from tension pneumothorax is the circulatory embarrassment caused by mediastinal displacement. Blumenthal and Neuhof emphasized the point that the tension in the pleural space might rise with dramatic suddenness causing symptoms of shock, cyanosis and circulatory failure. Little has been written on the method of treating tension pneumothorax. Blumenthal and Neuhof advised prompt measures to relieve the tension and to restore the mediastinum to its normal position. At the same time it is equally important to avoid a sudden opening of the pleural space to atmospheric pressure since there is in these cases a bronchopleural fistula and re-expansion of the lung will obviously be prevented. The best method would appear to be a gradual withdrawal of the air and lowering of the pressure in order to avoid the risk of the mediastinum suddenly swinging over with its attendant danger of mediastinal flutter, and to encourage re-expansion of the lung. Some of these points are illustrated in the following case history.

Case Report

The patient J.J.N., a girl, was born on July 31, 1951. She was admitted to hospital at the age of 7 months, on February 25, 1952.

Delivery was normal after a normal pregnancy. Her weight at birth was 7 lb. 6 oz. She was breast fed for seven months and was partly weaned on admission to hospital.

Twenty-four hours after birth the patient showed evidence of haemolytic disease, melaena and haematemesis. Rh-positive group O blood, 200 ml., was given intravenously. The condition cleared satisfactorily and the haemoglobin was 100% on the seventh day.

Both parents and their four older children were well at the time of the patient's admission to hospital.

The social conditions were unsatisfactory. Two rooms only were available for the whole family, one used as living room and the other as bedroom. There were three beds for the use of them all.

Five days before admission the patient suffered from a running nose. She was noticed to have a sore mouth and would not suck. Breathing became laboured 48 hours before she was admitted into hospital with a diagnosis of pneumonia. 'Sulphatriad' had been administered during the five days of her illness.

On examination in hospital the child was pale and toxic, and the alae nasi were acting vigorously with inspiration. Respirations were grunting. There was impaired respiratory excursion of the right side of the chest. The apex beat of the heart was seen to be half an inch outside the nipple line in the fourth intercostal space. On percussion, there was stony dullness of the right chest in front and behind. On auscultation, breath sounds were tubular over the right side of the chest.

On abdominal examination, the spleen was just palpable. Apart from purulent rhinitis, there were no other abnormal physical signs. The temperature on admission was 99°F, the respiration rate 60 and the pulse rate 140. A diagnosis of pneumonia with pleural effusion was made.

Pathological Investigations. Pus from the pleura was examined on two occasions. On February 26 the specimen was yellow, and a direct film showed debris, numerous degenerate cells and large numbers of Gram-positive cocci. On culture a profuse growth of *Staphylococcus aureus* (coagulase positive) was seen, and was penicillin- and streptomycin-sensitive.

The second specimen, also yellow, was seen on February 28. A direct film showed debris with large numbers of polymorph and mononucleated cells and numerous Gram-positive cocci. On culture there was a moderate growth of *Staphylococcus aureus* (coagulase positive). The organism was sensitive to penicillin, streptomycin, chloromycetin and aureomycin.

Blood cultured on March 6 showed no bacterial growth after eight days. On March 18 a full count gave Hb. 78% (11·5 g.%); leucocytes 12,000 per c.mm. (polymorphs, 6,960 or 58%, eosinophils, 240 or 2%, lymphocytes, 4,560 or 38%, monocytes, 240 or 2%).

Radiological Reports. On April 8 the pneumothorax was much smaller and was confined to the right upper zone, the right lung having re-expanded to fill the rest of the chest. The heart and mediastinum had returned to the mid-line and the herniation of the right pleura to the left side was not shown. A small amount of fluid remained at the right base (Fig. 5).

On May 7 the right lung was completely re-expanded with obliteration of the right costophrenic angle. There appeared to be some lipiodol residuum also. The eighth and ninth ribs had been resected surgically in the posterior axillary line (Fig. 6).

Treatment and Progress. On February 26 a paracentesis thoracis was performed and 75 ml. of thin, yellow, purulent fluid was aspirated, and proved the diagnosis of empyema. Penicillin, 750,000 units, was instilled into the pleural cavity.

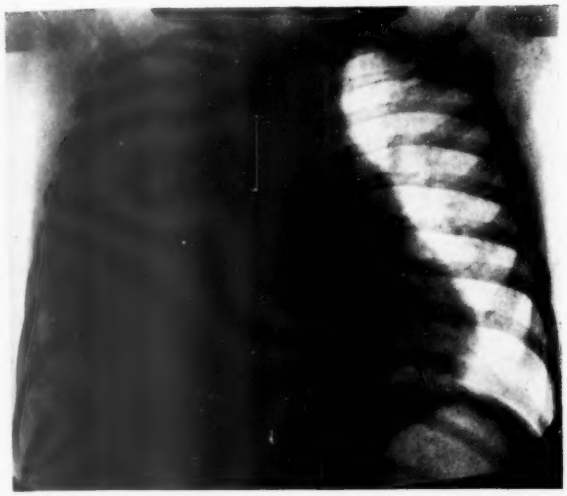

FIG. 1.—Radiograph demonstrating homogeneous opacity of the right side of the chest and the heart slightly displaced towards the left.

A radiograph (Fig. 1) of the chest showed a homogeneous opacity of the right chest, and the heart appeared to be slightly displaced to the left.

The patient was put on a course of penicillin starting on February 25, 500,000 units daily was given in divided doses six-hourly. This was continued until March 6. Streptomycin, 20 mg. per lb. body weight (estimated at 16 lb.) was also given daily from February 28 to March 6. Terramycin was given orally, 200 mg. daily from February 28 to March 6.

The pathological report of the pus taken on February 26 was that on culture there was a profuse growth of *Staphylococcus aureus*, coagulase-positive, penicillin- and streptomycin-sensitive.

Chest aspirations were performed daily. On February 27, 80 ml. thin pus was aspirated; on February 28, 58 ml. was aspirated and 125,000 units penicillin instilled; on February 29, 10 ml. of pus was aspirated, and 125,000 units of penicillin instilled.

The patient's clinical condition was improving. The temperature, which had ranged from 99° F. to 101° F., began to settle and fluctuations were less marked. Pus examined bacteriologically on February 28 gave the same organism which was sensitive to penicillin, streptomycin, chloromycetin and aureomycin.

On March 1 paracentesis of the chest failed to obtain any pus and it was thought that it was too thick to flow through the needle. A radiograph showed a collection of fluid as high as the fourth rib; there was a fluid level and air above it. Using 1% 'novocaine' as local anaesthetic, a vertical incision was made over the seventh or eighth intercostal space in the posterior axillary line and intercostal drainage was established by means of a rubber catheter (No. 6 Jacques). The skin was closed around the catheter and underwater drainage into a bottle of antiseptic solution at the bedside was employed. On each subsequent day 125,000 units of penicillin were instilled into the pleura via the intercostal drain until March 7. The empyema cavity ceased to drain and a de Pezzer type of catheter was inserted in place of the Jacques catheter.

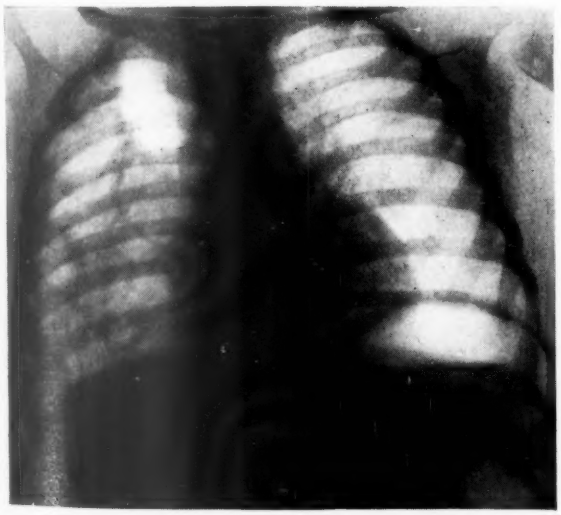

FIG. 2.—Radiograph during intercostal drainage and before instillation of lipiodol. There is a translucent area in the right upper chest.

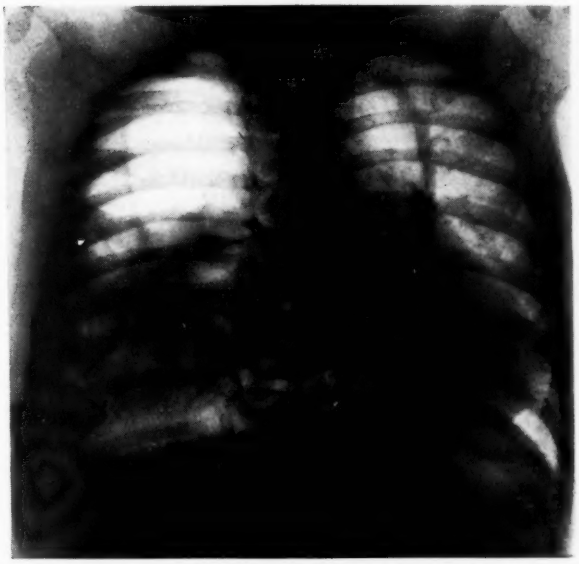

FIG. 3.—Radiograph during intercostal drainage showing a translucent area of the right upper chest extending over to the left side, and mediastinal displacement.

Figs. 2 and 3 are radiographs taken during the period of intercostal drainage.

In spite of the de Pezzer catheter, drainage continued to be unsatisfactory, and on March 18 about 5 ml. of lipiodol was run through the drainage tube into the

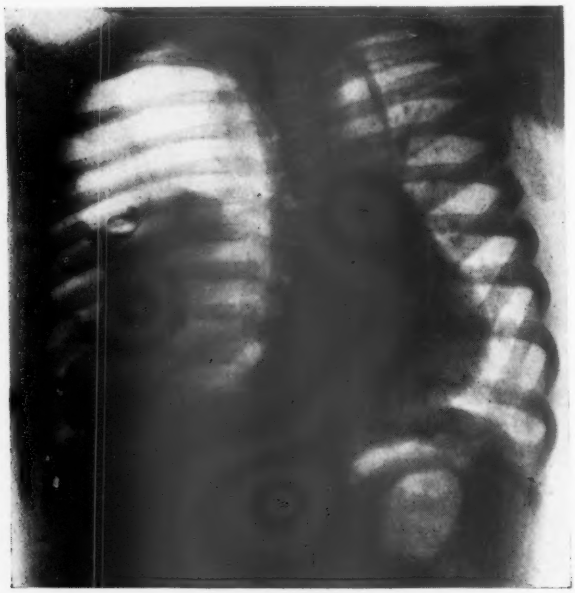

FIG. 4.—Radiograph after the instillation of lipiodol into the empyema. Blobs of lipiodol represent either loculations or pulmonary alveoli. A narrow channel communicates with the pneumothorax above.

pleural cavity by means of a record syringe using gentle pressure, and a radiograph was taken. Lipiodol was shown to be entering the right pleural cavity and to be filling what appeared to be loculations. The curious appearance of blobs of lipiodol was difficult to interpret. Loculations was one suggestion, another was a filling up of pulmonary alveoli. Careful study of the film taken on March 18 after lipiodol had been instilled also demonstrated a narrow channel leading upwards from the lower blobs of lipiodol, which seemed to enter an air-filled cavity occupying the right upper thorax. There was a small pool of lipiodol situated at the bottom of the cavity presenting a fluid level and a thin line of lipiodol creeping up the side of the cavity by surface tension. The upper half of the right side of the chest was completely translucent, strongly suggesting a pneumothorax. The translucent area extended across the mid-line to the left side of the chest. The whole of the mediastinum and the heart were markedly displaced towards the left side (Fig. 4).

At this stage very little pus was draining from the empyema tube and it was decided to establish free drainage by rib resection. This was performed on March 20. A de Pezzer catheter was stitched into the pleura. The skin was closed around the catheter which was led as before to an underwater drain. In spite of this there was still very little drainage from the pleura. Following the rib resection the child became pyrexial and a second course of streptomycin was given from March 21 to 31.

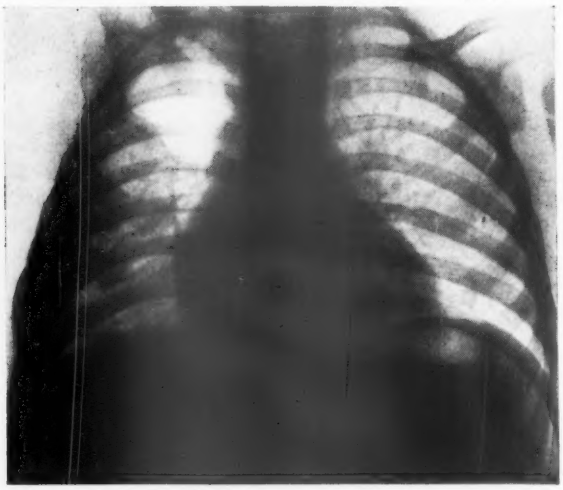

FIG. 5.—Radiograph after the release of air from the tension pneumothorax. The heart and mediastinum occupy normal positions.

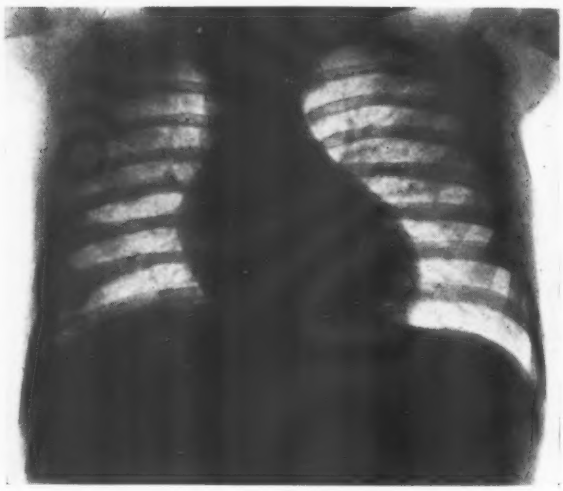

FIG. 6.—Radiograph showing complete re-expansion of the right lung.

Her condition remained unsatisfactory. Although the temperature was normal, she was cyanosed and obviously distressed. It was realized at this point that radiographs taken on March 18 were very strongly suggestive of a tension pneumothorax. Figs. 2 and 3 are radiographs taken on March 7 and 14 respectively. They were taken before the instillation of lipiodol. The radiograph of March 18 (Fig. 4) was taken after the instillation of lipiodol. All demonstrated the presence of a tension pneumothorax. The radiograph of March 14 demonstrated an adhesion crossing the right side of the pneumothorax from the upper portion of the collapsed right lung to the chest wall (Fig. 3).

Accordingly, on March 21, we began the release of the tension on the right side of the upper chest. A cannula was inserted into the third intercostal space anteriorly and attached to an artificial pneumothorax apparatus

based on the principle of Lillingston and Pearson. A pressure reading was taken at 8.30 p.m. The pressure excursion was very great. Air was released at intervals until the pressure was normal (see Table).

The tension pneumothorax seemed to re-accumulate air after each aspiration very slowly. The conclusion was that there was a bronchopleural fistula or a valvular communication from the empyema cavity to the upper pleura. No further drainage occurred from the empyema tube and this was removed on March 30. The sinus stopped discharging on about April 11.

Although there had been a history of only five days beginning with coryza, when the child was first seen in hospital an empyema thoracis had developed. The history suggested an upper respiratory infection going on to pneumonia followed rapidly by empyema, which was confirmed by paracentesis thoracis. The identification of *Staphylococcus aureus* completed the diagnosis. There was pyrexia during the first nine days, the morning and evening temperature reaching between 100 and 101° F.

The progress of the case might be conveniently divided into three phases. First, from the time of diagnosis until simple daily aspiration of the chest was abandoned, February 25 to March 1. The fluid was already purulent on admission and it was difficult to obtain adequate drainage by syringe aspiration, but it was possible to instill penicillin within the empyema cavity on three occasions.

Systemic chemotherapy extended into the second phase beginning when intercostal catheter drainage was instituted on March 1. At first, drainage under water was successful. Penicillin instillation was attempted, but failure to drain successfully necessitated frequent re-adjustments of the catheter. Lipiodol was run into the catheter and loculations of pus demonstrated and rib resection was undertaken. The patient was almost apyrexial during this period. There was an occasional temperature of 99° F. Following rib resection, the temperature rose but fever was controlled by giving streptomycin.

The third phase was from the time of recognition of the fundamental cause of the respiratory distress and cyanosis, i.e. the tension pneumothorax. This was released during the succeeding 10 days.

There is no doubt in retrospect that valuable time was lost in the second phase of the treatment (March 1 to 21). The intrapleural loculations interfered with drainage and prevented adequate penicillin instillations after the technique described by Fatti, Florey, Joules, Humphrey and Sakula (1946). Moreover, the presence of a tension pneumothorax was not recognized as early as it should have been.

The total time from intercostal drainage to the healing of the sinus was six weeks. Fatti *et al.* (1946) in 20 cases treated by a specially described technique of penicillin instillations through an intercostal drain, and compared with 14 controls obtained healing of the sinus three to six weeks after the beginning of drainage compared with an average of 11·6 weeks in the controls. The time from earliest pneumonic symptoms to healing of the sinus was seven weeks against 15 weeks in control cases untreated by pencillin instillations.

Once, however, adequate drainage was obtained by rib resection and loculations broken down and adequate steps had been taken to deal with the tension pneumothorax, recovery took place very quickly.

Summary

A case of tension pneumothorax and empyema

RANGE OF PRESSURE EXCURSIONS

Date and Time	Amount of Air Withdrawn (ml.)	Range of Pressure in Pleura*		Pulse		Respirations	
		Before (cm. water)	After	Before	After	Before	After
21.3.52 6.10 p.m.	325	+7/−9	+7/−8	130	150	40	50
8.30 p.m.	100	+9/−2	+8/−5	138	160	44	54
9.30 p.m.	100	+10/−5	+5/−5	130	164	44	54
10.30 p.m.	75	+7/−5	+5/−5	132	160	48	58
11.30 p.m.	125	+9/−2	+6/−4	142	150	48	54
22.3.52 10.30 a.m.	100	+10/−4	+4/−4	150	134	58	54
7.30 p.m.	175	+4/−6	+5/−5	146	154	50	56
23.3.52				Approximately	150	Approximately	50
24.3.52				Approximately	145	Approximately	35-58
25.3.52	175	+4/+2	−4/−8	140	148	32	48
26.3.52	0	−2/−8		128 to	140	26 to	48
30.3.52	10	+1/−4	−1/−5	126	138	26	38

* Normal intrapleural pressure is −7 cm. water in expiration, −14 cm. water in inspiration.

following primary staphylococcal pneumonia has been described.

It is pointed out that in cases of staphylococcal empyema it should be borne in mind that lung abscess, tension cyst, or tension pneumothorax is a distinct possibility. This helps in making an early diagnosis.

Treatment of the tension pneumothorax is described, making use of the Lillingston and Pearson artificial pneumothorax apparatus.

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HAEMANGIOENDOTHELIOMA OF THE LIVER SIMULATING CONGENITAL HEART DISEASE IN AN INFANT

BY

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The association in a young infant of persistent central cyanosis, increased by crying and feeding, with a systolic murmur heard all over the precordium, almost always indicates congenital heart disease. In the present case the existence of those features led to this diagnosis, yet the necropsy failed to reveal such a lesion. In fact the infant suffered from a haemangioendothelioma of the liver.

Case Report

M.H., aged 20 days, was admitted to hospital on account of dyspnoea and cyanosis. She had been normal at birth, apart from some blue asphyxia which quickly responded to treatment. Her birth weight was 7 lb. 13 oz.

Her mother said that the infant had always had difficulty in breathing, had seemed to breathe rapidly, and had tired easily during feeding. When 14 days old she had an attack lasting about 15 minutes, in which she became very blue and appeared to have difficulty in breathing. When 20 days old she had a similar attack which did not cease spontaneously. She was admitted to hospital about four hours after its onset.

On examination her nutrition was fairly good. She was too ill to weigh, but appeared to be average size for her age. There was moderate general cyanosis and the external jugular veins were slightly distended. The alae nasi were active. Her temperature was 99·6° F., pulse 180 (regular) and respirations 60. There were no congenital surface stigmata, no petechiae or naevi, and no clubbing of fingers or toes.

The left side of the thorax was slightly larger than the right; slight bilateral lower rib recession was seen. The cardiac apex beat was displaced to the left, just outside the mid-clavicular line. No thrill was felt in any area. The mitral sounds were spaced in even tapping rhythm. The pulmonary second sound was normal. A blowing systolic murmur could be heard all over the precordium, maximal at the middle of the lower end of the sternum. A short soft diastolic murmur was heard on both sides of the xiphisternum. The blood pressure was not taken. Femoral pulsation was normal. No subcutaneous oedema or serous effusion was observed.

Fine crepitations were present at both lung bases. The liver was enlarged by one fingerbreadth but there was no surface irregularity, pulsation or thrill. The spleen was not enlarged, and there was no undue abdominal distension.

FIG. 1.—Cut surface of the liver showing angiomatous masses appearing as pale, ill-defined nodules.

The cyanosis was slowly, but only partially, relieved in an oxygen tent; the heart rate fell to 150, and the respirations to 50 per minute.

A radiograph of the chest, taken by a portable machine, showed gross cardiac enlargement, mainly to the right, but also to the left, and slight vascular congestion of the lung fields. The pulmonary arteries were not visualized.

A full series of electrocardiograms gave a regular sinus tachycardia of 150 per minute and right ventricular hypertrophy in a vertical heart with clockwise rotation.

The tendency to cyanosis appeared to increase rapidly until it was possible to remove the baby from the oxygen tent for only a few moments at a time. X-ray screening was not practicable. Cyanosis then became extreme, and the child died eight days after admission.

Extract from Necropsy Report. There was no external evidence of congenital abnormality. The heart was considerably enlarged; both ventricles were hypertrophied, especially the right. The interventricular septum was intact. The foramen ovale was patent but largely covered by a crescentic fold of endocardium, and was normal for the baby's age; nothing in its appearance suggested a venous-arterial shunt. The valves and great vessels were normal, and the ductus arteriosus admitted a fine probe with difficulty and was clearly closing normally.

The lungs were greatly congested. The endocrine system was normal. The kidneys and spleen showed slight congestion. The brain and meninges were normal.

The liver was moderately enlarged. Most of the normal parenchyma was replaced by numerous nodules, each measuring about 1 cm. in diameter. These nodules were distributed throughout both lobes; some were visible on the surface and showed umbilication. No similar nodules were found elsewhere in the body. The gall bladder, extra-hepatic biliary tract and pancreas were normal. The alimentary system was otherwise normal.

HISTOLOGY. There was widespread replacement of the liver parenchyma by haemangioma. The nodules described above were composed of proliferating vasoformative cells and sinusoidal blood channels. The lungs, spleen and kidneys showed the features of venous congestion, but no other congenital abnormality was found.

In our case the diagnosis of congenital heart disease appeared to be fully justified before death. It seems likely that, as necropsy showed no such lesion, the heart failure was due to the arterio-venous shunt. It is interesting to note that in our case right-sided failure predominated, associated with cyanosis and venous engorgement. This has been noted in cases previously described, but usually other clinical features, such as cutaneous lesions, were present together with some of the clinical features described by Kunstadter (1933).

Pathological Considerations

Andries and Kaump (1944) classify haemangioma of the liver as (1) benign (large or small, single or multiple) or (2) malignant.

Stout (1943) has pointed out that theoretically malignant vascular tumours could arise from the endothelial cells, the perithelial cells, or the smooth muscle. The haemangioendothelioma is the commonest, the haemangiopericytoma has been described (Stout and Murray, 1942), but there is doubt about the leiomyosarcoma. A benign leiomyoma has been described (Stout, 1937, 1943).

Howard (1936) regards these lesions as multiple

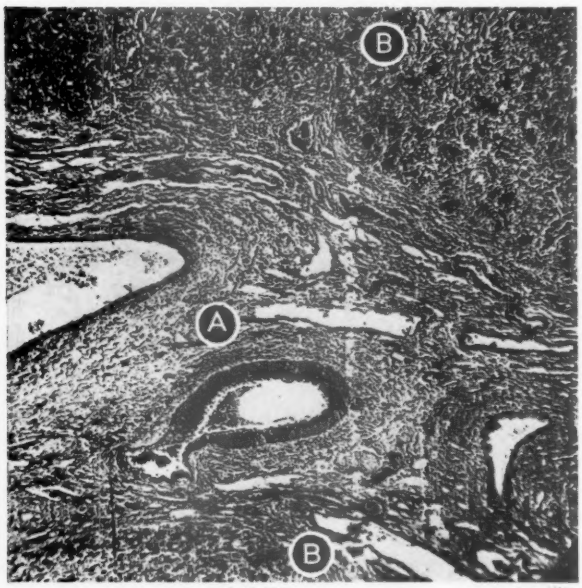

FIG. 2.—Section of liver (low power) showing portal tract (A) and liver lobules disorganized by proliferating vasoformative tissue (B).

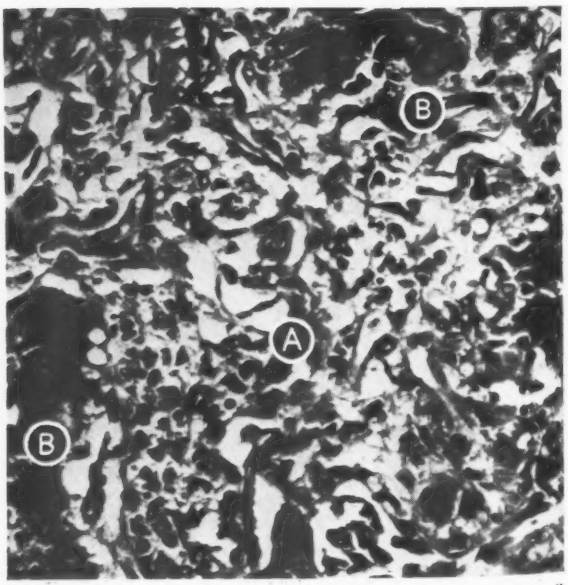

FIG. 3.—Section of liver (high power) showing vasoformative cells (A) separating the parenchyma into small, irregular groups of cells (B).

congenital tissue defects rather than malignant lesions.

A true hamartoma or vascular malformation is not a neoplasm; it has no power of disproportionate growth but enlarges with the tissues, apart from incidents such as haemorrhage or sepsis.

Foote (1919) considers all these lesions to be congenital, arising from endothelium which has not lost its embryonic characteristics. When this occurs in adults the benign angioma has either reverted to embryonic type or resulted from foetal inclusions. He recognizes a separate group of malignant tumours which probably occur mainly in adults.

Thus it is seen that there is controversy concerning the designation of the scattered lesions. The two points of view are, on the one hand, a primary malignant lesion with metastases, and, on the other, multiple congenital lesions. Rabson (1938) considers both explanations possible. We believe that a congenital tissue defect is the more likely explanation in our own case and probably in others arising in early infancy. Nevertheless, histological examination showed a degree of cellularity which one would associate with local malignancy, and in Fig. 3 the cellular elements can be seen infiltrating the liver cells.

Discussion

The term haemangioendothelioma was introduced by Mallory (1908) to describe a malignant vascular lesion of the skin but it has since been extended to include lesions elsewhere. Haemangioendothelioma of the liver has been described with and without similar lesions in other organs. Similarly haemangioendothelioma of various organs, yet without liver involvement, has also been described (Wollstein, 1931).

Kunstadter (1933) described a case of haemangioendothelioma of the liver in a child of 5 months, who had been noted to have an enlarged abdomen and pallor from the age of 6 weeks, and developed dyspnoea and cyanosis at the age of 4 months when lying down. Vomiting and constipation followed, and the infant died after laparotomy. Kunstadter reviewed 14 previously reported cases in infancy.

Cases have since been described by various authors, including Taylor and Moore (1933), Howard (1936), Dordick (1938), Schumann (1941), Blauel (1942), Andries and Kaump (1944), Schwartz (1945), Berezin, Scharnoff and Stein (1948) and Sweed and Weinberg (1950).

From the cases described in the literature it seems that the most constant presenting feature was abdominal enlargement, often accompanied by some gastro-intestinal disturbance such as vomiting, constipation or stool abnormality. Anaemia was a frequent finding, and jaundice and ascites were noted in two cases. A palpable abdominal mass, usually under the right costal margin, was noted in other cases. The condition of the infants deteriorated, and they usually died of exhaustion and respiratory embarrassment, sometimes with cyanosis.

Summary

A case of haemangioendothelioma of the liver is described in the neonatal period. Dyspnoea, feeding difficulty, central cyanosis, a systolic murmur, and a grossly enlarged heart suggested that a congenital heart lesion with heart failure was present. At necropsy there was no such lesion and the diagnosis was established.

We wish to thank Dr. N. F. Gowing who performed the necropsy and reported on the sections, and Professor T. Crawford of the Pathology Department, St. George's Hospital, London.

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THE INCIDENCE AND SIGNIFICANCE OF SYSTOLIC CARDIAC MURMURS IN INFANTS

BY

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In the course of carrying out routine physical examinations on newborn babies, certain infants were found who presented loud systolic cardiac murmurs in the absence of other abnormal physical signs. The significance of such a finding was doubtful, but the murmur in many cases was so loud as to suggest the possibility of congenital heart disease. An investigation was therefore carried out to assess the incidence and the significance of systolic cardiac murmurs occurring in the newborn.

Published records of such murmurs are few. Taussig (1947) has stated that 'a murmur audible in the newborn period is always of doubtful significance', but 'the persistence of a murmur for a period of weeks is usually indicative of a congenital malformation of the heart'. Siemsen (1938) examined newborn infants for the presence of cardiac murmurs at least twice a week during their hospital stay and found a wide variation in the incidence of murmurs. He placed the incidence as high as 25% of 105 infants examined, but the percentage with murmurs increased with the number of examinations per patient. These murmurs were systolic, mostly soft and blowing, and usually loudest over the apex. Lyon, Rauh and Stirling (1940) place the incidence of murmurs at 1·9% in a series of 7,673 newborn infants examined during the first week of life. The incidence appeared to be uninfluenced by such factors as sex of the infant, month of birth, birth weight and the occurrence of syphilis in the mother. They were able to follow the course of 92 infants with systolic murmurs in many cases up to 1 year of age. Four infants died, and two of these who came to necropsy were found to have congenital heart disease. Seventy-one infants were entirely normal, 14 had persistent murmurs, two had inconstant murmurs, and one had extrasystoles.

Cox (1948) has assessed the frequency of systolic murmurs as 5% of 630 'ostensibly healthy infants', but these were not all restricted to the newborn period. In just under half of the cases presenting murmurs the murmur persisted.

Method

The material for this investigation consisted of all newborn babies examined in the Simpson Memorial Maternity Pavilion, Edinburgh, over a five-month period from April to August, 1950. The total number of babies examined was 1,133. All examinations at birth and subsequent follow-up were carried out by one observer.

Each baby was subjected to a general clinical examination as soon as possible after birth. In particular the precordium was palpated for thrills and the heart auscultated at the four valvular areas. A chest piece 3 cm. in diameter, with diaphragm, was used for the auscultation. When a murmur was detected it was classified according to its intensity using the classification of systolic murmurs adopted by Levine and Harvey (1949). The classification was as follows:—

Grade I is the faintest murmur that can be distinctly heard (not likely to be audible during the first few seconds of auscultation). Grade II is a soft murmur that is heard immediately on auscultation. Grade III is a murmur louder than Grade II. Grade IV is a murmur louder than Grade III. Grades V and VI are the loudest of all and were not heard in this series. When any real doubt existed as to the presence of a Grade I murmur a negative finding was recorded and the baby examined on another occasion. No diastolic murmurs were detected in the series.

Repeated auscultation of the heart was carried out as often as could be arranged during the first 10 days of life, and in over three-quarters of the cases auscultation was carried out on two or more separate days within this period.

Radiographic and electrocardiographic examinations were carried out in the majority of babies with murmurs. The variable results of such examinations were difficult to assess, and seldom proved of real value in making a diagnosis of congenital heart disease in the neonatal period.

A group of 20 infants with systolic murmurs was

selected for a follow-up of two years' duration. Each case fulfilled both of the following conditions: (1) the presence of a Grade II, III, or IV murmur, (2) the detection of such a murmur on two or more successive days in the first 10 days of life. Most of these infants were examined at intervals of three months. The survivors were all re-examined at the age of 1 year and again at the age of 2 years.

Results

In 4·8% of the 1,133 babies examined a systolic murmur was audible during the first 10 days of life (Table 1).

TABLE 1

ANALYSIS OF BABIES IN PRESENT WITH AUDIBLE MURMURS

Maximum Grade of Murmur	Number of Babies with Murmur	Percentage of All Babies Examined
Grade I	18	1·6
Grade II	24	2·1
Grades III and IV..	12	1·1
	54	4·8

In all cases the intensity of the murmur was maximum along the left border of the sternum, or at the pulmonary or mitral areas. In 12 cases the murmur persisted throughout the neonatal period. In other cases the murmur was transient, appearing within a few days of birth and lasting for one, two, or three days.

In only a few cases the systolic murmur was associated with other abnormal physical signs. Thus in two infants suffering from erythroblastosis foetalis the cardiac murmur appeared when the haemoglobin level fell below 75% and disappeared when the haemoglobin was restored above this level by therapeutic measures. In two other cases a Grade I systolic murmur, which disappeared after a few days, was associated with extrasystoles.

There was no significant difference between the group of murmurs and those without as regards sex, weight or associated diseases.

Two babies who did not present systolic murmurs during the neonatal period died, and were proved to have congenital heart disease at necropsy. One died within two days of birth from interventricular septal defect, dextroposed aorta, stenosis of the pulmonary artery, and congenital atresia of the oesophagus. The other appeared normal during the neonatal period. He developed a loud systolic murmur by the age of 6 weeks and died at the age of 8 weeks. Necropsy revealed an adult type of coarctation of the aorta.

The results of the two-year follow-up of 20 infants is given in Table 2.

TABLE 2

TWO-YEAR FOLLOW UP OF 20 INFANTS WITH SYSTOLIC MURMURS

Children apparently normal	14
Died with evidence of congenital heart disease at necropsy	2
Died with no evidence of congenital heart disease at necropsy	1
Murmurs persisting at 2 years of age	3

In 10 of the 14 children who are now apparently normal the murmur did not persist beyond the neonatal period. In two the murmur persisted to 3 months of age, and in two it persisted to 1 year before disappearing.

Of the two babies with evidence of congenital heart disease at necropsy, one died at the age of 11 days with cor triloculare and a large foramen ovale. The other died at the age of 6 weeks with a bicuspid aortic valve and aortic valvular stenosis.

A provisional diagnosis of congenital heart disease has been made in each of the three children who survive with loud systolic cardiac murmurs. One is thought to be suffering from coarctation of the aorta, another from a patent interventricular septum and the third from aortic stenosis.

Conclusions

The results of this investigation are in agreement with the experience of other observers. The differences in the recorded incidence of systolic murmurs in the newborn are probably due to the subjective nature of the examination required to detect their presence, but 2 to 5% of infants present such murmurs. The majority of these murmurs must be due to 'physiological' causes as they usually disappear by the age of 3 months but occasionally persist to the age of 1 year. Possible physiological causes are the patency of the foramen ovale and the ductus arteriosus. According to Christie (1930) the foramen ovale has closed in 95% of infants and the ductus arteriosus in 99% by the age of 1 year. In 14 of the 20 children followed up to the age of 2 years in the present series the murmur had disappeared by the age of 1 year, whereas in each of the three children with persistent murmurs a diagnosis of congenital heart disease has now been made.

The intensity of the murmur does not appear to be of any diagnostic value, as the loud Grade III or Grade IV murmurs may disappear within a few days or weeks. A consideration of the intensity of the murmur combined with its persistence may be of some value. Thus the soft transient systolic murmur

is the one least likely to be associated with congenital heart disease. The infant with a loud persistent systolic murmur is more likely to be suffering from congenital heart disease, but in the absence of other diagnostic evidence the diagnosis may remain in doubt until after the age of 1 year.

Summary

In the examination of 1,133 newborn infants systolic murmurs were detected in 54 (4·8%).

Periodic observation of a selected group of 20 infants with murmurs revealed that in 14 the murmur had disappeared by the age of 1 year. In three infants loud systolic murmurs have persisted to the age of 2 years, and a provisional diagnosis of congenital heart disease has been made in each case. Two infants in the group died and necropsy revealed evidence of congenital heart disease. In a third infant who died there was no evidence of congenital heart disease at necropsy.

I wish to thank Professor R. W. B. Ellis for advice in the preparation of this paper, and Dr. A. R. MacGregor for the necropsy reports.

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IDIOPATHIC RENAL ACIDOSIS IN TWINS

ALKALOSIS RESULTING FROM OVERDOSAGE OF A CITRATE MIXTURE

BY

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The literature and theories of the causation of idiopathic hyperchloraemic renal acidosis of infants have recently been reviewed by Latner and Burnard (1950). They describe the biochemical findings and give experimental evidence to show that the probable cause of the condition is faulty absorption of bicarbonate from the proximal tubules of the kidney. There is at present no evidence to show whether the disease is congenital or acquired but the former is more probable. The present description of the condition occurring in twins lends weight to this view.

Summary of Clinical, Biochemical and Necropsy Findings

The clinical features of the condition can be summarized as failure to gain weight, vomiting, constipation and hypotonia. In severe cases there is often a report that the child passes an abnormally large quantity of urine, and dehydration may be a prominent feature. The syndrome most commonly begins about the weaning period.

On laboratory investigation it is found that the urine is persistently alkaline (Payne, 1948) and often contains a few pus cells. In contrast to this, however, the child is in gross acidosis, the plasma bicarbonate being below 30 vol. CO_2% (13·5 mEq./litre) and the chloride raised. The blood urea level is often at the upper limits of normal.

At necropsy pathological findings are limited to the kidneys. These organs cut with a gritty sensation and radial calcification is seen in the medulla. On microscopy the calcification is found to be confined to the collecting tubules. It is best demonstrated by x-ray films of the kidneys taken after death. Theoretically it should also be visible in the x-ray films of the abdomen taken during life, and in gross cases this may be possible. Usually, however, the degree of calcification is not sufficient for it to be visualized, especially as the intestines are often full of gas.

Case Reports

The occurrence of the condition in twins is recorded below. They were studied at the Department of Child Health, Welsh National School of Medicine, Cardiff. This is believed to be the first time that the condition has been recorded in two members of one family. One of these twins died of a respiratory infection probably aided by too large a dosage of citrate mixture.

Case 1. Susan P., a twin, was delivered at full term (birth weight 5 lb.). She received cow's milk for the first six weeks, then the feed was changed to artificial dried milk. The child had received orange juice but no codliver oil.

There are five siblings, including a step-sister and the twin sister. None of the other children has had any illnesses in infancy or other relevant diseases, nor have any relatives had anything similar.

Apart from bronchitis at 3 weeks, progress was satisfactory until the age of about 6 months. The baby was first seen at the age of 8 months with a six weeks' history of 'taking feeds badly'. She would not suck from a bottle, but would take out of a cup. The milk was changed from National Dried Milk to cow's milk without any improvement. She was constipated and passed one or two hard motions a day. Urine was voided freely.

On examination the child was a small, pale infant, who appeared dehydrated and had obviously lost weight. On admission her weight was 15 lb. 5 oz. compared with her highest known weight of 18 lb. 6 oz. at the age of 6 months. The abdomen was scaphoid and the liver just palpable. The limbs were hypotonic. Nothing abnormal was detected in the chest or heart. A clinical diagnosis of idiopathic renal acidosis was made.

The following investigations were made before treatment was begun.

The urine was persistently alkaline (*p*H 7·5) and contained some pus cells. On one occasion a few colonies of *Staphylococcus aureus* were grown; two days later, however, another specimen was found to be sterile.

A blood count gave haemoglobin, 12·6 g. (85%); red blood corpuscles, 4·4 m. per ml.; white blood corpuscles, 22,800 per ml. (neutrophils, 65%, lymphocytes, 25%, monocytes, 10%). The blood urea level was 40 mg. per 100 ml.

A radiograph of the chest and abdomen revealed no significant abnormality. The Mantoux test (1:1,000) was negative.

The plasma bicarbonate level was 26 vol. CO_2%, and plasma chloride 750 mg. %.

The child had a temperature of 97° F. on admission, but on the next day it rose to 99° F., falling again to normal on the fourth day. Therapy with the sodium

citrate-citric acid mixture was begun on the evening of the sixth day and one dose of 60 ml. was given. The temperature by that time had risen to 102° F. Two further doses of 60 ml. each were given the next day and the temperature continued to rise to 104° F. and remained between 103° and 104° until the child died. On the seventh day after admission she developed convulsions, nystagmus and a right external rectus palsy. A catheter specimen of urine was normal. Further blood investigations showed a plasma bicarbonate level of 76 vol. CO_2 % and plasma chlorides level of 695 mg. %. Unfortunately this result was not known until the evening, by which time the third dose of citrate mixture had been given. The child's condition continued to deteriorate, convulsions being almost continuous despite 2 ml. of paraldehyde intramuscularly. On the eighth day blood investigations gave a plasma bicarbonate level of 81 vol. CO_2 % and a plasma chloride level of 759 mg. %.

The cerebrospinal fluid showed no abnormality.

The baby was given 5% glucose in water intravenously, intramuscular penicillin, 100,000 units three-hourly, and a total of 3 ml. of paraldehyde intramuscularly. Breathing became very distressed, and the trachea was sucked out under direct vision by Dr. J. Haley, a large quantity of mucopus being removed. Despite this, the child died in the early morning of the ninth day after admission.

NECROPSY. A necropsy was performed by Dr. D. B. Richards.

The right lung contained an area involving the posterior one-third of the upper and lower lobes which was of a uniform greyish-red. The left lung had a similar appearance. Microscopy of these areas revealed extensive bronchopneumonia.

Both kidneys were of normal size, and cut with a gritty sensation. The cortex was normal in appearance, but there were extensive foci of calcification outlining the periphery of the pyramids. On microscopy the calcification was seen to be confined to the collecting tubules.

Case 2. Christine P. was the twin of Susan P. (birth weight 5 lb. 8 oz.).

She was fed on National Dried Milk at first, later on cow's milk. Progress was satisfactory until the age of 7 months. The child then lost her appetite, started to vomit frequently, and became constipated. There was no history of passing abnormal quantities of urine.

On examination the child seemed rather small for her age (weight 16 lb. 8 oz.). There was no gross wasting or dehydration, but an extreme degree of hypotonia was apparent. Nothing abnormal was detected in the heart, lungs, abdomen, or central nervous system.

Before treatment the urine had a *p*H of 7·4. The plasma bicarbonate level was 29 vol. CO_2 % and the plasma chloride level 666 mg. %.

The child was started on 45 ml. per day of the citric acid-citrate mixture, and, after an initial loss, rapidly gained weight. Twenty days later the plasma bicarbonate was 43 vol. CO_2 %. Her general condition had improved and she had lost the hypotonia. Unfortunately she then developed a suppurative otitis media which proved somewhat resistant to treatment. She continued to gain weight well, however, and after a fortnight weighed 18 lb. 10 oz. The plasma bicarbonate level was then 36 vol. CO_2 % and serum chlorides 674 mg. %.

After discharge from hospital the child developed Sonne dysentery and lost weight again. Following this she gained weight well, but was found to be anaemic (haemoglobin 5 g. or 35%). The biochemistry gradually returned to normal, and apart from what appeared to be a febrile convulsion on one occasion she has remained well. She no longer requires the medicine, and appears to be a normal child both clinically and biochemically.

Discussion

It is very regrettable that when Susan P. died it was not appreciated that she was a twin. The other child at that time was apparently normal. It has, therefore, not been possible to prove that they were identical twins. The following factors are significant. They were always regarded as being identical and had to be dressed differently to distinguish them as babies. A photograph taken of the two children together reveals a striking similarity. When seen in hospital Susan had been ill for some weeks and Christine was still well so the resemblance was less obvious.

The causation of idiopathic renal acidosis has been very briefly referred to above. The fact that it can occur in twins indicates that it may be congenital in origin, but there is no evidence so far to suggest that it is a genetically determined condition.

A second point which emerges from consideration of these cases is the danger of overdosage with the citrate mixture; the following formula was used:

Citric acid . . . . 60 g.
Sodium citrate . . . . 100 g.
Water to 1,000 ml.

The initial dose should be about 45 ml. per day and may be increased as required.

The clinical and biochemical findings in Susan P. are very similar to those of a case recorded by Payne (1950). Both children had convulsions due to the profound alkalosis and both showed hyperelectrolytaemia, having a high blood chloride as well as the raised plasma bicarbonate.

Summary

Idiopathic renal acidosis in twins (probably identical) is described. One child developed hyperelectrolytaemia and bronchopneumonia following overdosage with the citrate mixture. The danger of this potent therapeutic weapon is stressed.

I wish to thank Professor A. G. Watkins for permission to publish these cases. I would also like to thank the pathologists who performed the biochemistry and Dr. D. B. Richards for the necropsy findings.

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TREATMENT OF THE SCHOENLEIN-HENOCH SYNDROME WITH ADRENOCORTICOTROPHIC HORMONE (A.C.T.H.) AND CORTISONE

BY

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It has been shown that a relationship exists between the Schoenlein-Henoch syndrome and diseases such as acute nephritis, rheumatic fever and polyarteritis nodosa (Gairdner, 1948). In view of this relationship, it seemed reasonable to try the effect of adrenocorticotrophic hormone (A.C.T.H.) and cortisone on the course of this disease. It was hoped also that these hormones might reduce the incidence of glomerulonephritis, which was found by Philpott (1952) in 47·5% of 40 cases in children studied, and which is considered the most dangerous complicating feature of this syndrome.

Only a few reports have appeared in the literature on the treatment of the Schoenlein-Henoch syndrome with A.C.T.H. and cortisone. Stefanini, Roy, Zannos and Dameshek (1950) treated one case with A.C.T.H. Although this patient's general condition improved remarkably, there were further attacks of purpura while the patient was being treated and a relapse of all symptoms occurred when it was stopped. Nephritis, which was present before starting the A.C.T.H., deteriorated while under treatment. Woolley (1952) reported a case treated with A.C.T.H. in which further symptoms occurred while under treatment and pre-existing nephritis deteriorated. Kugelmass (1951) reported four cases treated with cortisone and was enthusiastic about its value. He did not state, however, how frequent or how complete were the urinalyses in these cases, and did not make clear how long these patients were under surveillance. Kugelmass admitted that 'mild manifestations' might continue for weeks after the withdrawal of the drugs.

We have treated nine children with the Schoenlein-Henoch syndrome with A.C.T.H. or cortisone or both. The results are presented, two cases being reported in full and summaries given of the remaining seven.

Case Reports

Case 1. The patient, a girl, was aged 5 years in March, 1951. For five days she had had swollen joints and a rash for four days with colicky abdominal pain and blood in the stools. The rash was typical of the Schoenlein-Henoch syndrome but there was no arthritis on admission. For 12 days she continued to pass bloody stools and further crops of skin lesions appeared. Intramuscular injection of A.C.T.H. was then started and continued for 25 days, a total of 475 mg. being given. The eosinophil count was always too low to assess any depression during treatment. The child's general condition rapidly improved on treatment and the intestinal bleeding ceased in two days. Several crops of skin lesions appeared during the first week of treatment, after which all symptoms ceased. The urine showed evidence of acute nephritis on the day A.C.T.H. treatment was begun. She still has evidence of nephritis but there have been no further symptoms.

Case 2. A boy, aged 3 years in May, 1951, had otitis media six weeks before admission. During the succeeding weeks this was followed by periodic swellings of the joints and a rash which was most marked over the buttocks and limbs. During the last 10 days before admission he had been passing frank blood per rectum as well as melaena stools. He was admitted on May 9, 1951.

On admission he appeared a well nourished, slightly febrile child (99° F.) not acutely ill. A papulo-purpuric rash was present on the face, buccal mucosa, buttocks, arms and legs. He had a small subconjunctival haemorrhage in the left eye. The left elbow and wrist were slightly swollen and tender. He also had acute tonsillitis and a right submental abscess. He passed a melaena stool shortly after admission.

Haemoglobin was 10·0 g. %; platelets, 450,000 per c.mm. Capillary fragility was positive at −250 mm. Hg. Blood pressure was 106/70 mm. Hg. The erythrocyte sedimentation rate was 8 mm. in one hour.

The child was given intramuscular penicillin and the right submental abscess was incised. On May 11 fresh petechiae appeared on the arms and he complained of central abdominal pain. He passed several stools containing frank blood. Treatment with A.C.T.H. was begun in a dose of 10 mg. six-hourly. On May 13 he was much livelier, the rash was fading and the stools were macroscopically normal. The eosinophil count had fallen from 27 to 2 per c.mm. by the end of five days. Six days later, on May 17, a new batch of A.C.T.H. was begun and the

dose was reduced to 5 mg. six-hourly. On May 19, associated with a strongly positive Mantoux reaction (O.T. 1/1000), fresh skin lesions appeared. The batch of A.C.T.H. was altered and the dose was increased to 10 mg. six-hourly, but further petechiae continued to appear. The drug was continued until May 26. He received a total course of 570 mg. Subsequently it was shown that the batch of A.C.T.H. used from May 17 to May 26 may have been inactive as it failed to produce any eosinophil response in a control case. During the subsequent three months without treatment the patient continued to have further skin eruptions.

On admission the boy's urine and E.S.R. were normal. On May 22, following an exacerbation of the purpura, protein (250 mg. %) appeared in the urine and red blood cells and granular and cellular casts were seen. The urinary changes persisted for 10 weeks and then gradually returned to normal. The E.S.R. was raised during this time, but subsequently became normal. His blood pressure was never higher than 120/75 mm. Hg. An Addis count on February 22, 1952, was within normal limits. He is being observed as an out-patient and remains clinically well.

Case 3. A boy, aged 10 years in April, 1951, had abdominal pain for five weeks and for four weeks swollen joints and a rash. On admission he had the typical rash of the Schoenlein-Henoch syndrome, blood in the stools, and the right wrist was swollen. His general condition was very good, but the E.S.R. was 30 mm. in one hour and the urine showed evidence of acute nephritis. Intramuscular A.C.T.H. was started on the day after admission, producing a good eosinophil response. The intestinal bleeding and arthritis subsided, and no fresh skin lesions appeared for 10 days, when an extensive crop was produced. This coincided with the use of a new batch of A.C.T.H. which, it was considered, might be inactive (see Case 2). In 14 days 440 mg. of A.C.T.H. had been given, and, as fresh skin lesions were still appearing, treatment was altered to cortisone which was given for five days (total 500 mg.). There were no further symptoms during treatment but he has had several attacks of purpura since. The nephritis was unaffected by treatment and is still present.

Case 4. A girl, aged 6 years in October, 1951, for two days had had swollen joints and a rash for one day. On admission, she was ill, had the typical rash, and the left wrist and both elbows were swollen. A.C.T.H. was given intramuscularly for a week (total 315 mg.) without any eosinophil depression. Her general condition slowly improved and the arthritis subsided in two days and did not recur. Further skin lesions appeared almost daily for two weeks, after which there were no further symptoms. After another three weeks she was found to have acute nephritis but this subsided in a further three weeks, the final Addis count being normal. She has remained well since.

Case 5. A boy, aged 2 years in November, 1951, suffered an attack of rash and swollen joints in August, 1951, lasting 10 weeks. After four weeks' freedom the symptoms recurred and he was admitted on the fourth day of the relapse. He was ill, and had an extensive maculo-papulo-petechial rash and subconjunctival haemorrhages, but there was no arthritis. Further skin lesions appeared for a week when a stool contained blood. At this stage intramuscular A.C.T.H. was started and given for six days (total 480 mg.). His general condition improved slowly but two days after starting treatment a further bloody stool was passed and more skin lesions appeared. After this there were no further symptoms. The eosinophil response was not studied in this case. He has remained well since and there has been no evidence of nephritis.

Case 6. A girl, aged 3¾ years in November, 1951, had had for nine days a rash and swollen joints. On the day before admission she passed a bloody stool and vomited. On admission she was ill, and had the typical rash but no arthritis. Intramuscular A.C.T.H. was started on the day after admission and continued for six days (total 480 mg.). A satisfactory eosinophil response was obtained. Her general condition rapidly improved and she had no further symptoms. The urine was at no time abnormal. She has remained well since.

Case 7. A boy, aged 10½ years in January, 1952, had had a rash and swollen joints for eight days. He had had severe abdominal pain without blood in the stools for the first two days of the illness. On admission he was ill and in considerable pain from arthritis. Both knees and ankles were swollen and he had an extensive maculo-papulo-petechial rash. Intramuscular A.C.T.H. was started on the day of admission and continued for six days (total 480 mg.). The eosinophil count was always too low to assess any depression. No further skin lesions appeared during treatment and the existing arthritis rapidly subsided. His general condition rapidly improved, but on the day after starting treatment the right wrist became swollen and two days later the left wrist also became involved. Both subsided in 48 hours. Further skin lesions appeared, associated with some abdominal pain, on the day after A.C.T.H. therapy was discontinued. He had no further symptoms and has remained well since. At no time has the urine shown any abnormality.

Case 8. A girl, aged 2 years in January, 1952, came to hospital with a four-day history of a rash appearing over the extensor surfaces of the limbs and over the buttocks. Three days before admission areas in the centres of the spots appeared to ulcerate. One day before admission she passed fresh blood per rectum. On the day of admission (January 20, 1952), the arms and legs became swollen, and she was unable to stand.

On admission she was an extremely ill child with a fever of 101·8° F. with a severe papulo-purpuric rash over the face, buttocks, arms and legs with ulceration of the centres of some of the larger lesions, especially those on the buttocks with many petechiae between the larger lesions. The elbow, knee and ankle joints were painful and swollen; the metacarpal and interphalangeal joints were also swollen. There was some oedema of the right eyelid, and pitting oedema of the upper and lower limbs. Apart from tachycardia (140/min.) no other abnormality was detected.

Haemoglobin was 9·1 g. %, white blood cells were 23,000/c.mm. and platelets 360,000/c.mm. The erythrocyte sedimentation rate was 8 mm. in one hour. The blood pressure was not recorded. A blood culture was negative.

On the day after admission the eyelids and joints were more swollen. She was extremely ill and lethargic. Treatment with A.C.T.H. was begun on January 22. The first four doses were 25 mg. given at six-hourly intervals. The effect on the eosinophil count could not be recorded as this count was never greater than 1 per c.mm. Thereafter 10 mg. were given six-hourly. She received a total of 300 mg. in six days. Four hours after A.C.T.H. was begun the eyelids were so oedematous that they were completely closed, and she appeared moribund (Fig. 1). Her temperature was 104° F. Her condition

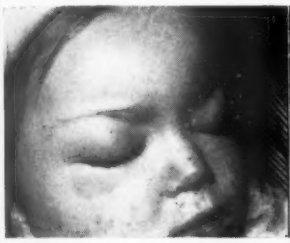

FIG. 1

FIG. 2

was worse than on admission, for although the joint swellings were slightly less marked, the oedema of the eyelids had increased and there was oedema of the face and neck. Twenty-four hours later there was a marked improvement; the rash was fading, the swellings of the joints had gone, and the facial oedema was lessening. On January 24 she was sitting up playing with toys, and on January 26 the face was normal (Fig. 2). On this day, however, she again became miserable, and slight oedema of the legs and arms reappeared. There was no return of the arthritis. Further petechiae appeared on January 27, but no further frank blood was seen in the stools.

Cortisone, 12·5 mg. intramuscularly six-hourly, was started on January 27 and continued for 10 days (total 500 mg.). After the first 24 hours no marked improvement was noted and not until January 30 did the oedema subside once more. From then on she made an uninterrupted recovery. No further rash, joint swellings or oedema developed while she was on cortisone and there were no relapses after discontinuing treatment. She was discharged on February 15, 1952, and out-patient surveillance has been continued.

On admission the urine was normal. On January 24 it contained 70 mg. % of protein, 4-6 red blood cells per high power field and granular casts. Since then repeated specimens have been normal. The E.S.R. has never been raised above 12 mm. in one hour and the blood pressure has remained normal.

Case 9. A girl, aged 7 years in January, 1952, had abdominal pain, swollen joints and a rash for four days. On admission, she was not acutely ill. She had an extensive rash and arthritis involving both wrists and ankles and the right elbow. Cortisone was started two days after admission, 120 mg. being given orally in the first 24 hours, followed by 460 mg. intramuscularly during the subsequent six days. A satisfactory eosinophil response was produced. Her condition improved over the following two days and the rash and arthritis subsided but after another two days she had a further bout of abdominal pain and fresh skin lesions appeared. At the same time the urine showed evidence of acute nephritis. Since then she has had no further symptoms, but she has persistent proteinuria and the E.S.R. remains elevated.

Discussion

In this series of cases six were given A.C.T.H. alone, and two received A.C.T.H. followed by cortisone because of relapses. One case was given cortisone alone. The potency of the hormones was judged by the response of the circulating eosinophils and seems to have been adequate in most cases. In only one case was no fall encountered, but the count was too low to assess any fall in three cases. The response was not studied in one case. The results of treatment are summarized in Table 1.

The effect of the hormones on the general condition was assessed by the recovery of well-being, the disappearance of irritability and the return of appetite. Five patients showed considerable improvement within 48 hours, and three more improved more slowly. One patient (Case 3) was not sufficiently unwell to assess any change in the general condition. The constitutional upset during the Schoenlein-Henoch syndrome may be severe, and in Case 8 caused considerable alarm. A rapid improvement was seen on A.C.T.H. therapy, only to be followed by a relapse. Improvement in these cases may have been due to the hormones, but similar improvement can occur spontaneously.

Six cases presented joint swellings and in five the swelling subsided within three days of starting treatment. In one case joint swellings recurred during treatment. Intestinal bleeding occurred in six cases but was seen in only one case after starting hormone therapy. In the natural course of the disease in children, however, joint swellings and intestinal bleeding seldom recur (Philpott, 1952), and the hormones, therefore, were of doubtful value.

The skin manifestations recurred in eight cases during treatment. One batch of A.C.T.H. used in Cases 2 and 3 was thought to be inactive, but further skin lesions appeared in both cases after changing the batch in one and giving cortisone instead in the other. The hormones were, therefore, useless in preventing these manifestations.

The diagnosis of nephritis was made on persistently finding protein, red blood cells and casts in the urine. One patient developed this complication before treatment and in another it was discovered

TABLE 1

EFFECTS OF TREATMENT WITH A.C.T.H. AND CORTISONE IN THE SCHOENLEIN-HENOCH SYNDROME

Case	Treatment	Effects of Treatment				Nephritis	
		General Improvement	Joint Swelling	Intestinal Bleeding	Rash	Before Treatment	After Treatment
1	A.C.T.H.	Rapid	Present before admission; absent on admission; no recurrence	No recurrence	Recurred	Present	Present
2	A.C.T.H.	Rapid	Subsided; no recurrence	No recurrence	Recurred	Absent	Present
3	A.C.T.H. and Cortisone	Not assessed	Subsided; no recurrence	No recurrence	Recurred	Present	Present
4	A.C.T.H.	Slow	Subsided; no recurrence	Absent	Recurred	Absent	Present
5	A.C.T.H.	Slow	Present before admission; absent on admission; no recurrence	Recurred	Recurred	Absent	Absent
6	A.C.T.H.	Rapid	Present before admission; absent on admission; no recurrence	No recurrence	No recurrence	Absent	Absent
7	A.C.T.H.	Rapid	Recurred	Absent	Recurred	Absent	Absent
8	A.C.T.H. and Cortisone	Rapid—relapse —slow	Subsided; no recurrence	No recurrence	Recurred	Absent	Absent
9	Cortisone	Slow	Subsided; no recurrence	Absent	Recurred	Absent	Present

during the first 24 hours of treatment. Three developed it during, or shortly after concluding, hormone therapy. This course is not different from that seen in untreated cases. Nephritis, if it developed, was not appreciably influenced by treatment, and so the hormones were valueless in preventing or treating this complication.

It is concluded that A.C.T.H. and cortisone were of no value in treating our cases of the Schoenlein-Henoch syndrome. Their use should probably be considered only in cases with a severe constitutional disturbance.

Summary

Nine cases of the Schoenlein-Henoch syndrome are presented in which treatment with A.C.T.H. and/or cortisone was given. No dramatic results were encountered. The drugs did not prevent relapses in the condition the onset of nephritis in three of seven cases, neither did they have any effect on the course of the nephritis. We were not convinced that the drugs were of any value in our cases.

We wish to thank Professor R. S. Illingworth and Professor E. J. Wayne for allowing us to study cases under their care, and for their helpful criticism and advice.

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THE URINARY EXCRETION OF HISTAMINE IN CHILDREN

BY

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The role of histamine in disease has long been a subject of speculation but until recently little was known about its metabolism because of difficulties in estimating the free, pharmacologically active form in body fluids (Gaddum, 1948, 1951). However, new methods for the separation and purification of histamine have made it possible to follow its excretion in the urine, where it occurs in free and conjugated forms (Anrep, Ayadi, Barsoum, Smith and Talaat, 1944; Roberts and Adam, 1950). Conjugated histamine, which is pharmacologically inactive, is mainly acetyl histamine (4(β-acetylaminoethyl)-imidazole) and is formed by bacteria in the gut (Urbach, 1949).

In adults the excretion of free histamine changes little from day to day but that of the conjugate varies between wide limits. When histamine is given by slow intravenous infusion, about 1% of the dose appears in the urine as free histamine and there is no detectable increase in the urinary conjugate. After oral administration, however, it appears in the urine mostly in the conjugated form (Adam, 1950). These facts suggest that the normal excretion of free histamine in the urine may represent the continuous formation or liberation of histamine in the tissues and that the excretion of the conjugate is related to the amount of free histamine in the alimentary tract.

Little is known about the metabolism of histamine in childhood, and the object of the present investigation was to determine whether infants and children excrete histamine and, if so, the form and quantity in which it occurs. At the same time we investigated the urinary excretion of histamine in infantile gastro-enteritis, since it has been suggested that the absorption of histamine from the intestine causes symptoms in this condition (Mellanby, 1916).

Selection of Children for the Investigation

Since reliable 24-hour specimens of urine can only be obtained from children under close supervision by trained nursing staff, the specimens of urine were collected from children in the wards and convalescent homes of the Royal Hospital for Sick Children, Edinburgh. Strictly speaking, therefore, the children were convalescent; the majority had recovered from minor respiratory infections; a few had been admitted for investigation of vague symptoms for which no cause had been found; others had healed fractures and were being kept in hospital for remedial exercises. Some of the infants had been in hospital with gastro-enteritis, but all had fully recovered and were ready to go home.

All the children were on normal diets and none was receiving drugs. Children with a history or family history of allergic diseases, and unduly fat or thin children, were not selected. The subjects of this investigation, therefore, can reasonably be considered as healthy children.

Urine from infants with gastro-enteritis was collected at the gastro-enteritis unit of the City Hospital for Infectious Diseases, Edinburgh. The first specimen was collected as soon as possible after admission from male infants with symptoms and signs of severe gastro-enteritis; that is to say, every infant was passing frequent, loose, green stools and showed signs of dehydration. The disease was of the endemic type, since no epidemic occurred during the period of the investigation. While the urine was being collected the infants were given Hartmann's solution, by mouth or by intravenous drip, and either sulphadiazine or chloramphenicol by mouth. In each case the second collection was made one week after the first. By this time all the infants were on milk feeds and were passing normal stools.

Pharmacological Methods

Extraction of Histamine. The method used was that of Roberts and Adam (1950), whose paper should be consulted for full details.

FREE HISTAMINE. Free histamine is separated from conjugated histamine and other substances in 50 ml. of urine by adsorption on a column of the cationic exchanger

'decalso F' (the Permutit Co., London). The histamine is then eluted by treating the column with concentrated ammonium hydroxide followed by chloroform saturated with ammonia gas. After evaporation of the eluent under reduced pressure the residue is taken up in 10 ml. of 0·9% NaCl and neutralized; in this way the histamine is concentrated fivefold. By this method, the mean recovery when histamine is added to various body fluids in the range of 0·5 to 5μg is 67%±1·1. This fraction is a characteristic of the decalso column and a correction can be applied to the results; in the present paper, the results are uncorrected.

CONJUGATED HISTAMINE. Urinary percolate, 10 ml., from the decalso column is applied to a column made of charcoal and sand. The charcoal adsorbs the conjugated histamine along with other substances and acid alcohol is used as the eluent. The purification thus achieved is only partial. The eluent is evaporated to dryness and the residue boiled in concentrated HCl to hydrolyse the conjugate. After evaporation of the acid the residue is taken up in 0·9% NaCl, neutralized, and made up to 10 ml. The mean recovery when 2·5 μg of acetyl histamine is added to 5 ml. of urine is 82%±2·4.

Estimation and Identification of Histamine. The histamine values are all calculated in terms of the base on the assumption that this represents 36·16% of the weight of the phosphate. The extracts were tested on a strip of guinea-pig ileum suspended in 2 ml. of Tyrode's solution containing atropine (0·1 μg per ml.) and were compared with a standard solution of histamine acid phosphate (British Drug Houses, Ltd.). Mepyramine maleate (May and Baker, Ltd.) in a concentration of 2×10^{-8} was added to the bath at the end of the assay.

Clinical Methods

Owing to the difficulty of obtaining reliable 24-hour specimens of urine from females, all the children selected were males. The urine was collected in chemically clean bottles of 600 ml. capacity, each of which contained 3 ml. of 2N HCl to ensure that the specimen was kept at less than *p*H 4. After collecting into one bottle for 12 hours this bottle was stored at 0°C., and the collection continued for a further 12 hours in a second bottle. Samples for bacteriological examination were taken from each bottle before pooling the whole 24-hour specimen. The extraction of histamine was started in every case within six hours of completing the collection.

In the older children the urine was passed directly into the bottle by means of a funnel fixed in the neck. Infants were placed on a metabolic bed and the urine passed down through tubing into a bottle below the bed. Various types of collecting apparatus were tried at first but were all discarded in favour of Paul's colostomy tubing of 1 in. width, which was strapped with adhesive strapping to the infant's penis. This tubing is very light and no trouble from kinking or backflow was encountered owing to its wide lumen and easily distended wall. Since the collections lasted for only 24 hours, the disadvantages of the prolonged use of strapping did not arise. The tubing was washed thoroughly before use as the powdered chalk in new tubing was found to adsorb histamine.

Results

The healthy children were divided into four groups according to their body weight at the time of collection. These groups correspond roughly to the following age groups: 1 year and under, 2 to 5 years, 6 to 9 years, and 10 to 12 years. The results are presented in Table 1, and those for the free histamine are also shown graphically in Fig. 1. The results obtained in the infants with gastro-enteritis are contained in Table 2. The first five of these infants received chloramphenicol during the acute stage of the illness; the next four, sulphadiazine; and the last infant, no drug treatment.

When the histamine equivalent for the conjugate in extracts of infants' urine was less than 0·01 μg/ml., the amount of conjugate is shown as less than the value calculated from the threshold dose of the standard solution of histamine. These values therefore varied with the sensitivity of the strips of ileum in the assays. In our calculations we have assumed that no histamine was present in these samples.

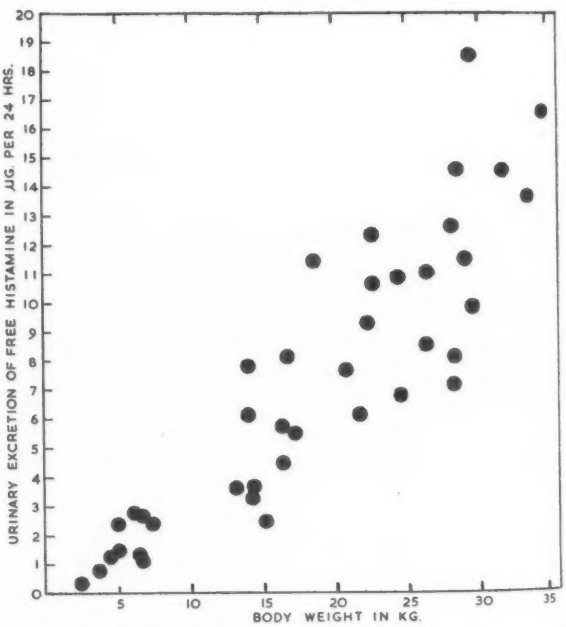

FIG. 1.—Results for free histamine in healthy children.

We have also expressed the 24-hourly excretion of histamine in μg. per kg. of body weight but only the mean values and the range are given in the table.

Fig. 2 shows the inhibitory effect of mepyramine maleate on equiactive doses of the standard solution of histamine and of an extract of infant's urine from the decalso column. The fact that the rate of recovery

TABLE 1

EXCRETION OF HISTAMINE IN FOUR GROUPS OF HEALTHY INFANTS

I			II			III			IV		
Body Weight (kg.)	Histamine in Urine (μg./24 hrs.)		Body Weight (kg.)	Histamine in Urine (μg./24 hrs.)		Body Weight (kg.)	Histamine in Urine (μg./24 hrs.)		Body Weight (kg.)	Histamine in Urine (μg./24 hrs.)	
	Free	Conj.		Free	Conj.		Free	Conj.		Free	Conj.
2·3	0·3	2	13·2	3·6	3	18·6	11·4	33	28·2	7·2	9
3·7	0·8	3	14·1	6·1	13	20·9	7·6	24	28·2	8·1	28
4·5	1·3	6	14·1	7·8	14	21·8	6·1	9	28·2	12·6	14
5·0	1·5	3	14·3	3·3	31	22·3	9·3	15	28·6	14·5	16
5·0	2·4	<2	14·5	3·7	7	22·7	10·6	5	29·0	11·5	24
6·1	2·8	5	15·2	2·5	17	22·7	12·3	14	29·5	9·8	15
6·4	1·3	<2	16·4	4·5	5	24·5	6·8	93	29·5	18·5	20
6·7	1·1	<3	16·4	5·7	8	24·5	10·8	15	31·8	14·5	46
6·8	2·7	4	16·8	8·1	14	26·4	8·5	25	33·6	13·6	120
7·3	2·4	<6	17·3	5·5	47	26·4	11·0	9	34·9	16·5	114
Mean											
5·4	1·7	2·3	15·2	5·1	15·9	23·1	9·4	24·2	30·1	12·7	40·6

Conjugate calculated as histamine

		I	II	III	IV
Excretion of free histamine (μg./kg. per 24 hrs.)	Mean	0·30	0·33	0·42	0·42
	Range	0·13–0·48	0·16–0·55	0·28–0·61	0·25–0·63
Volume of urine excreted in 24 hours (ml.)	Mean	349	539	712	1050
	Range	148–600	410–650	475–1030	780–1700
Concentration of free histamine in urine (μg./litre)	Mean	5·30	9·37	14·38	12·23
	Range	1·5–16·2	5·3–13·9	6·1–24·0	7·9–17·4

for the extract is the same as that for the standard strengthens the evidence that the activity of the extract is due to histamine. A further test consisted in boiling an extract from the decalso column for one hour in concentrated HCl and comparing its activity with that of an unboiled extract of the same urine. The histamine equivalents of these extracts agreed to within 10%.

TABLE 2

URINARY EXCRETION OF HISTAMINE IN ACUTE AND CONVALESCENT STAGES OF INFANTILE GASTRO-ENTERITIS

Infant	Free Histamine (μg. per 24 hrs.)		Conjugated Histamine* (μg. per 24 hrs.)	
	Acute	Convalescent	Acute	Convalescent
W.H. ..	1·0	2·4	<2	<10
E.L. ..	0·5	1·2	3	<4
P.O'K. ..	2·8	3·2	<6	<8
A.R. ..	0·7	0·7	<3	9
J.R. ..	0·5	1·2	1	2
D.W. ..	1·0	0·6	<5	<5
S.H. ..	1·0	2·2	3	5
J.G. ..	0·6	0·6	2	3
N.R. ..	1·2	0·9	18	<5
B.S. ..	1·6	3·3	9	<3
Mean ..	1·1	1·6	3·6	1·9

*Calculated as histamine.

The specimens were collected under clean but not sterile conditions, and therefore samples of urine

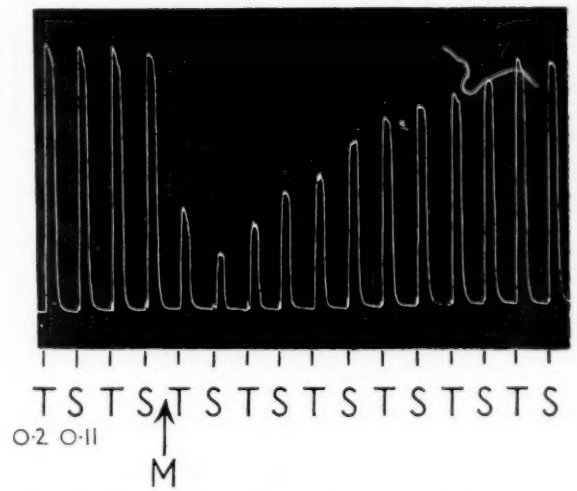

FIG. 2.—Responses of guinea-pig ileum to equiactive doses of urine extract (T) and histamine standard (S, 0·1 μg/ml.). Test solution was 50 ml. infant's urine extracted on a decalso column and concentrated fivefold.
Arrow represents addition of 0·2 ml. mepyramine maleate (concentration 2×10^{-8}). Time interval between doses, 90 secs.

taken just before extraction were cultured. No growth occurred in the majority of cases but six showed a few colonies of bacteria and five showed a moderate growth of *Bact. coli*. In no case was the urine infected before collection and there was no evidence that the bacteria cultured had any effect on the values obtained for free or conjugated histamine.

Discussion

Infants and young children excrete free and conjugated histamine in the urine. It is evident that as the body weight increases so does the 24-hourly excretion of free histamine. This relationship is less definite for the conjugate, the values for which are more widely scattered. As the average weight rose from 5·4 kg. to 30·1 kg. the amount of free histamine rose from 1·7 to 12·7 μg. per 24 hours. When the excretion was calculated as μg./kg./24 hours the mean for the two heavier groups ($0·42 \pm 0·026$)* was significantly ($P < 0·05$) higher than the mean for the two lighter groups ($0·315 \pm 0·023$). Nevertheless the results are thought to justify the use of this method of calculation and to show that it is more likely to give more consistent results than any other simple method. This conclusion is supported by calculations based on the results of Roberts and Adam (1950) who found that the average 24-hourly excretion of free histamine by five healthy adult males was 21·6 μg. These authors did not record body weights but if we assume that the mean body weight of these men was 70 kg., their excretion of free histamine was 0·31 μg./kg. This suggests that the excretion of free histamine is directly proportional to the body weight not only during growth but also after it has stopped.

Infants excrete only minute quantities of the conjugate: this is consistent with the excretion that might be expected with a milk diet. Anrep *et al.* (1944) found in the rat and dog that diets of milk and casein had no effect on the excretion of conjugated histamine, whereas meat or histamine given by mouth greatly increased it. Again, it is possible that the bacterial flora in the alimentary tract of infants is poor in organisms that acetylate histamine.

The fact that in all the children the excretion of free histamine is less variable than that of the conjugate lends additional support to the view that the free histamine derives mainly from the tissues and the conjugate from the alimentary tract. On this view, the normal excretion of free histamine is likely to have some physiological meaning but that of the conjugate is not.

* Standard error of the mean

Histamine in Gastro-enteritis

The theory that the symptoms of gastro-enteritis in infants are caused by the absorption of toxic bacterial products formed in the gut has been advanced repeatedly (Jeans and Marriott, 1947; Ivy, 1948; Kerpel-Fronius, 1948). Mellanby (1916) was the first to suggest that histamine might be one of these products, since it was known that the alimentary tract contained bacteria which could decarboxylate histidine in culture. Many organisms which decarboxylate histidine in this way have since been identified in the faeces of healthy adults, but there is no evidence that they occur in significant numbers in the intestinal contents of infants with gastro-enteritis (Gale, 1940, 1944).

Histamine is normally present in the faeces in the free and conjugated forms (Myhrman and Tomenius, 1939; Urbach, 1949): some of the free histamine is probably destroyed by histaminase in the intestinal mucosa and some of the conjugate is absorbed but produces no symptoms because it is inert. If, on Mellanby's view, histamine causes toxic effects after it is absorbed, we must assume that appreciable quantities of free histamine reach the circulation unchanged, either because unusually large amounts are formed in the intestine, or because it is no longer conjugated or destroyed. In the dog various agents, such as chloroform and alcohol, promote the absorption of histamine after they have been applied directly to the mucosa of the gut (Mammoser and Boyd, 1929). They may act either by dissolving histamine or by interfering with its inactivation or in other ways. It is conceivable, on this analogy, that inflamed gut, as compared with healthy gut, allows histamine to pass more freely into the circulation. When histamine is given by slow, intravenous infusion it is more easily detected in the urine than in the blood, probably because it is concentrated in the kidneys (Adam, 1950). Hence the passage of free histamine from the gut into the general circulation in amounts large enough to produce the symptoms of gastro-enteritis would be expected to increase the amount excreted in the urine. In the present investigation the difference between the amount of free histamine excreted in the acute stage of gastro-enteritis and the amount excreted by the same child after recovery was not significant. The results, therefore, do not support the view that the absorption of histamine from the alimentary tract is a cause of symptoms in infantile gastro-enteritis.

Summary

The urinary excretion of histamine has been investigated in 40 healthy children.

Children excrete histamine in free and conjugated forms. The rate of excretion of free histamine was approximately proportional to the body weight and varied from 0·30 to 0·42 μg./kg./24 hours.

The urinary excretion of histamine was also investigated in 10 infants with gastro-enteritis in the acute stage and during convalescence. The difference between the mean values at each stage was not significant.

We wish to thank the consulting staff of the Royal Hospital for Sick Children and Dr. A. Joe, Medical Superintendent of the City Hospital, for permission to investigate patients in their wards and also the nursing staff at these hospitals without whose willing cooperation this work could not have been carried out. We are grateful to Professor J. H. Gaddum, F.R.S., for criticism, and to Mr. R. P. Stephenson, of the Pharmacology Department, for generous help with the construction of an apparatus for the assays.

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THE ABSORPTION OF CHLORAMPHENICOL IN THE NEWBORN

BY

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The increasing prevalence of penicillin-resistant organisms, particularly staphylococci, in neonatal infections has led to the wider use of the more recent antibiotics. The absorption of one of these, chloramphenicol, has been studied in adults (Ley, Smadel and Crocker, 1948) and in children (Kelly, Hunt and Tashman, 1951; Ross, Burke and Rice, 1952). There is, however, no adequate published information on this subject in the newborn. At this age antibiotics are often given more or less prophylactically for quite minor infections, so that the problem of the correct dosage cannot be resolved by clinical results. The alternative is to give an amount which maintains a plasma level in excess of the *in vitro* sensitivity of the organisms. As there are good reasons for supposing that the absorption of the drug may be different in the first 10 days of life, the previous studies on children and older infants have been repeated for this age group. The investigation is based on 173 observations on 68 infants. Reports of cases of aplastic anaemia following the use of chloramphenicol (Gill, 1950; Wilson, Harris, Henstell, Witherbee and Kahn, 1952) have accentuated the need for a more cautious and informed administration of the drug.

Materials and Method

A microbiological assay was used employing a strain of El Tor vibrio which was completely inhibited by a concentration of 0·5 μg. per ml. The method is essentially that of Gray (1952), which is in turn a simplification and improvement of the original technique of Doorenbos and Kop (1951). A stock culture was maintained on a plain agar slope incubated aerobically at 37° C., subcultures being made approximately weekly.

Administration. The palmitate suspension was given just before the feed either by spoon or in a bottle diluted with an equal amount of expressed breast milk or dried milk mixture. The crystalline preparation was individually dispensed and added to the feed as a powder. No difficulty was experienced in giving the drug in either form, but a number of infants receiving the higher doses of both preparations vomited after 24 to 48 hours of the course and continued until the drug was stopped. No other suggestions of toxicity were encountered, but in two cases not included in the trial oral thrush developed after 48 hours on doses of approximately 25 mg. per kg. six-hourly. In one of these *Monilia* was also found on a buttock rash.

Sampling. All assays were performed upon 1 ml. venous samples taken into sterile tubes containing 200 I.U. of dried heparin. These were then centrifuged and the plasma withdrawn. Where possible the assay was completed forthwith, but specimens which had to be kept overnight were stored at −28° C.

Assay. For the actual estimation a convenient dilution (solution A) of the plasma was made. This was 1 in 10 where the anticipated levels were below 20 μg. per ml., and 1 in 15 or 1 in 20 when higher levels were expected. For this purpose a 0·04 ml. constant drop Dreyer pipette was used, held vertically, delivering at the rate of one drop per second. The diluent was Armour peptone water (*p*H 7·2) with 1% dextrose and 1% Andrade's indicator added. The diluted plasma was then heated in a water-bath for 20 minutes at 60° C., thus destroying the normal inhibitory action of plasma on the growth of the vibrio (Doorenbos and Kop, 1951). Serial dilutions of solution A were then made with Dreyer pipettes in sterile 3 in. by $\frac{3}{8}$ in. test tubes, using the same diluent. Ten tubes were used, the first containing 10 drops of A and none of peptone water, the second nine drops of A and one of peptone water, and so on until the tenth tube, which contained one drop of solution A and nine of peptone water. Two control tubes each containing 0·4 ml. of diluent were also set up with each batch. All tubes except one of the controls were inoculated with a 5 mm. diameter wire loopful of an overnight growth of the vibrio in plain peptone water. The cultures were incubated at 37° C. for 18 hours. Where growth occurred the culture became pink. The tube containing the lowest concentration of chloramphenicol which inhibited growth was taken to contain 0·5 μg. per ml.

The sensitivity of the organism was titrated against known concentrations of pure crystalline chloramphenicol in plain peptone water at intervals throughout the trial, although not with each batch of readings. In

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all cases the organism was completely inhibited at a concentration of 0·5 μg. per ml. and grew at 0·4 μg. per ml.

Results and Discussion

The blood levels recorded at intervals after different doses of both crystalline and palmitate chloramphenicol are shown in Tables 1 and 2. The number of venipunctures on any one infant were deliberately limited. Infants who regurgitated or vomited part of any dose have been excluded.

These figures confirm the wide range in the rate and degree of absorption of the drug that has been a feature of previous studies on older infants and children. The levels two hours after administration of the crystalline preparation were of the same order as those found by Kelly *et al.* (1951); however, in the newborn, they appeared to be maintained for longer, and where the dose was repeated six-hourly maximum concentrations were attained in 24 hours. At this interval 25 mg. per kg. maintained levels substantially in excess of 10 μg. per ml., which is the minimal inhibitory concentration *in vitro* for the majority of susceptible organisms (Bliss and Todd, 1949). In most of the cases this level was attained in two hours.

Chloramphenicol palmitate was absorbed more slowly, less effectively, and over a longer period than the crystalline form. Plasma levels in general above 10 μg. per ml. could be maintained by a dose of 25 mg. per kg. six-hourly. Such a dose would be incapable of effecting an adequate therapeutic level in the first few hours. This could be accomplished in most cases, however, by giving an initial dose of 100 mg. per kg.

TABLE 1

RESULTS WITH CRYSTALLINE CHLORAMPHENICOL

Dose (mg./kg.)	Plasma Levels† (μg./ml.)			
	2 Hours	6 Hours	10 Hours	24 Hours
25	<5·0	<5·0		
	<5·0	<5·0		
	* 5·5	<5·0		
	* 8·3	8·3		
	*10·0	6·3		
	12·5	8·3		
	*15·0	16·6		
	16·6	7·1		
	16·6	8·3		
	*16·6	10·0		
	*25·0	16·6		
50	6·3	5·5	<5·0	
	10·0	5·5	<5·0	
	*12·5	16·6		
	*15·0	12·5		
	16·6	16·6	8·3	
	16·6	16·6	10·30	
	*16·36	16·36		
	*16·36	12·35		
	*25·30	16·36		
	25·30	25·30	25·30	
	20·30	20·30	Contd. six hrly.	25·30
	35·30	50·30	,,	50·30
75	11·31	12·35		
	14·33	20·30		
	16·36	33·33		
	20·30	33·33		
	25·30	50·30		
	24 Hours	48 Hours	72 Hours	
25 every six hours	14·3	20·0		
	16·6	16·6		
	20·0	20·0		
	25·0	25·0	33·3	
	33·3	20·0	16·6	

* These samples are from premature infants, all of whom weighed over 31 lb. 8 oz.

† Except where otherwise stated the levels are following a single dose.

TABLE 2

RESULTS WITH CHLORAMPHENICOL PALMITATE

Dose (mg./kg.)	Plasma Levels* (μg./ml.)			
	2 Hours	6 Hours	10 Hours	24 Hours
50	< 5·0	7·1		
	< 5·0	8·3		
	< 5·0	12·5		
	< 5·0	5·5	< 5·0	
	<10·0	5·0		
	5·0	5·0		
	8·3	10·0	7·1	
	16·6	12·5		
Six hourly	< 5·0	<10·0	8·3	25·0
Six hourly	< 5·0	7·1	10·0	25·0
100	< 5·0	< 5·0	10·0	7·1
	< 7·5	7·5		
	5·0	7·1	10·0	
	6·25	10·0	6·25	5·0
	6·3	16·6	12·5	5·0
	8·3	6·3		
	8·3	10·0	8·3	< 5·0
	10·0	10·0		
	10·9	15·0		
	12·5	18·75		
	15·0	16·6		
Six hourly	5·0	5·0		16·6 (12·5 at 48 hours)
Six hourly	16·6	12·5		25·0
Six hourly	5·0	10·0		25·0 (50·0 at 48 hours)
150	<10·0	<10·0	<10·0	
	10·0	12·5	14·3	
	10·0	14·3	12·5	
	10·0	16·6	16·6	
	12·5	16·6	16·6	
	20·0	33·3	16·6	
	24 Hours	48 Hours	72 Hours	
100 then 25 six hourly	5·0	5·6	10·0	
	6·26	16·6	8·3	
	7·5	15·0	15·0	
	7·5	15·0		
	12·5	10·0	16·6	

* Except where otherwise stated the levels are following a single dose.

Summary and Conclusions

Crystalline chloramphenicol was more quickly and completely absorbed in the newborn than the palmitate form, the use of the latter offering no particular advantages.

A dosage of 25 mg. per kg. of the crystalline preparation six-hourly, and 100 mg. per kg. of the palmitate initially followed by 25 mg. per kg. six-hourly, is suggested.

I wish to thank Professor A. A. Moncrieff for permission to carry out these investigations on infants under his care, and also Dr. J. D. Gray for the strain of El Tor vibrio and for his help and advice. Messrs. Parke Davis and Co. kindly supplied both the chloramphenicol palmitate and the pure crystalline chloramphenicol for standardization.

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DIAGNOSTIC PNEUMOPERITONEUM

BY

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The use of a pneumoperitoneum to visualize abdominal viscera is an obvious and well recognized procedure. In the case described the method was used in a child in whom a radiological opacity was seen in the left thorax, and it enabled a definite diagnosis to be made.

Case Report

B.C., aged 5 years and 8 months, was admitted with the complaint of cough, loss of weight and recurrent sore throats. There had been an uncertain quantity of thick sputum and he had been lethargic and easily tired. He had occasional pain below the left nipple.

He had had pneumonia at 3 months, recurrent bronchitis, measles at 3 years and pneumonia at 4 years.

There was nothing relevant in the family history.

The child was admitted to another hospital in 1951 and was found to have opaque antra. A radiograph of the chest revealed a shadow at the left base which was thought to be due to an encysted diaphragmatic left pleural effusion. A second opinion was that the left lobe of the liver was bulging through a weakened area of diaphragm.

The boy was admitted to the Victoria Hospital in July, 1951, for further investigation. The blood count was normal and the tuberculin jelly test was negative.

Figs. 1, 2 and 3 are reproductions of some of the films taken, and show a rounded shadow surrounded in the first figure by an area of pneumonitis.

Air, 1,000 ml., was introduced into the peritoneal cavity, using the Lillingstone and Pearson apparatus with a Saugmann's needle. Local anaesthetic was used and the puncture was made through the left iliac fossa, mid-way between the umbilicus and the anterior superior spine. After 1,000 ml. had been introduced the abdomen was distended and tympanitic, but the child suffered no discomfort.

FIG. 1.—Loss of translucency in the left lower zone due to consolidation.

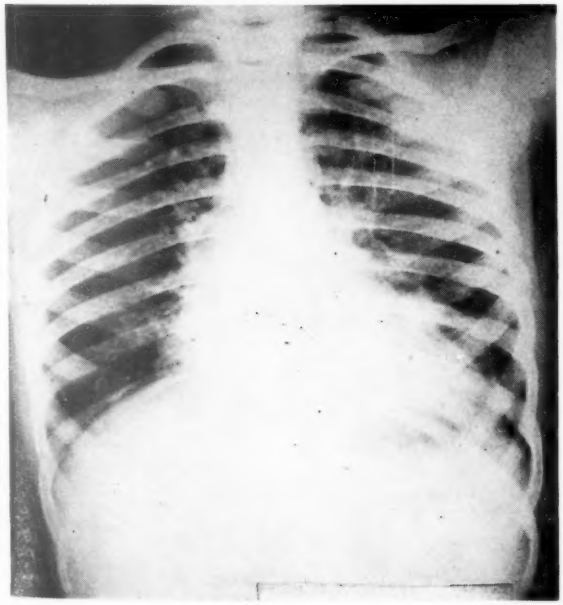
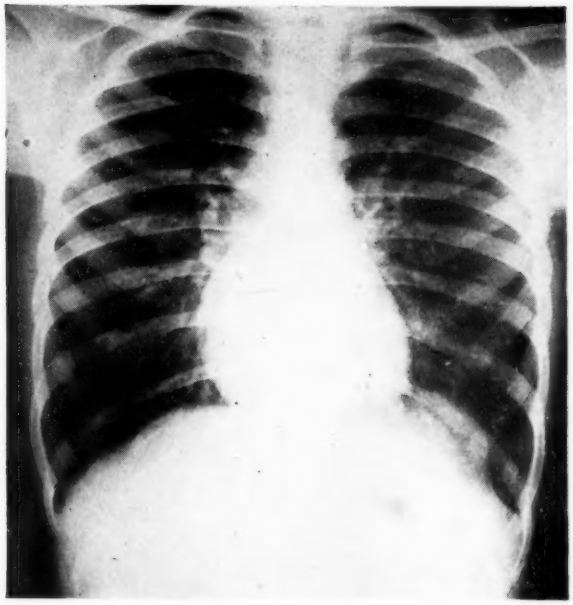


FIG. 2.—Later film showing that consolidation has resolved leaving a hump shadow above the left diaphragm.



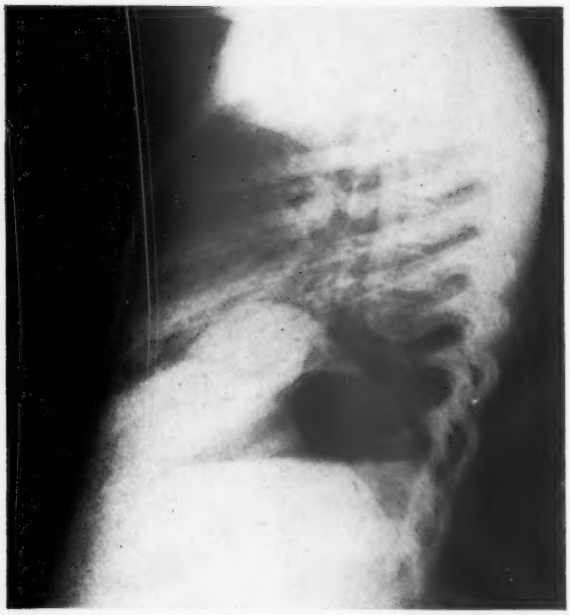


FIG. 3.—The hump shadow visualized in the left lateral position.

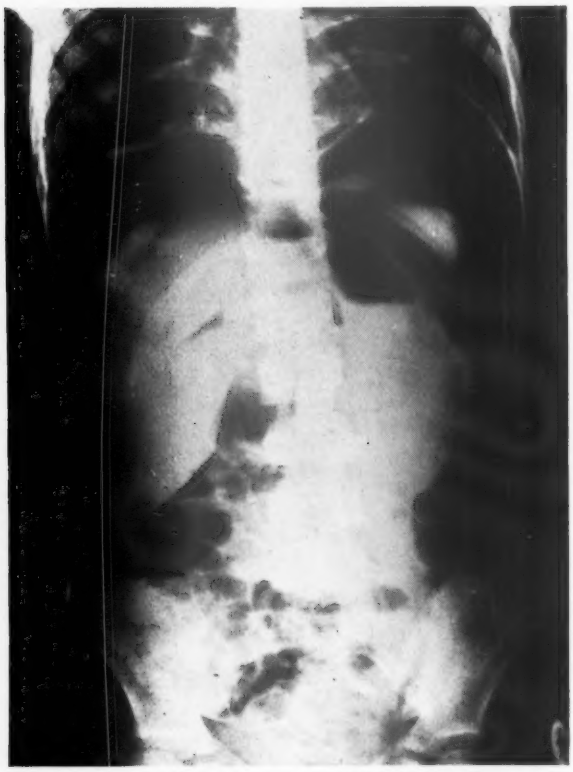


FIG. 4.—Pneumoperitoneum reveals shadow to be a diaphragmatic bulge.

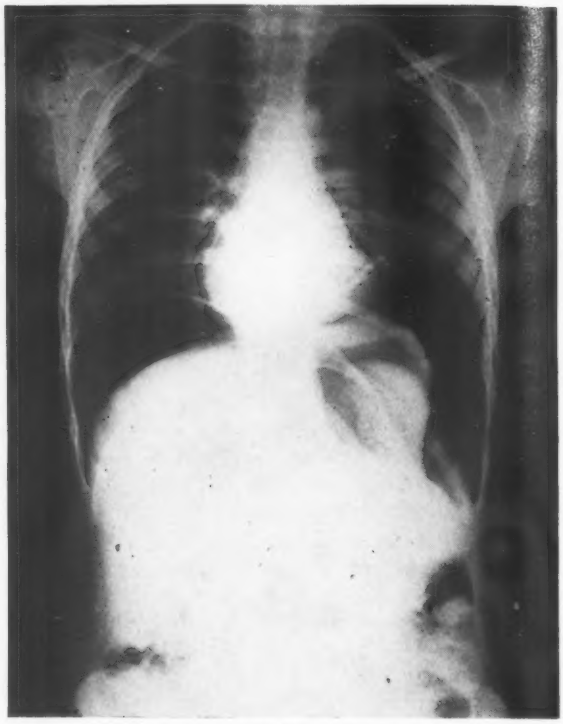


FIG. 5.—Further postero-anterior view after pneumoperitoneum.

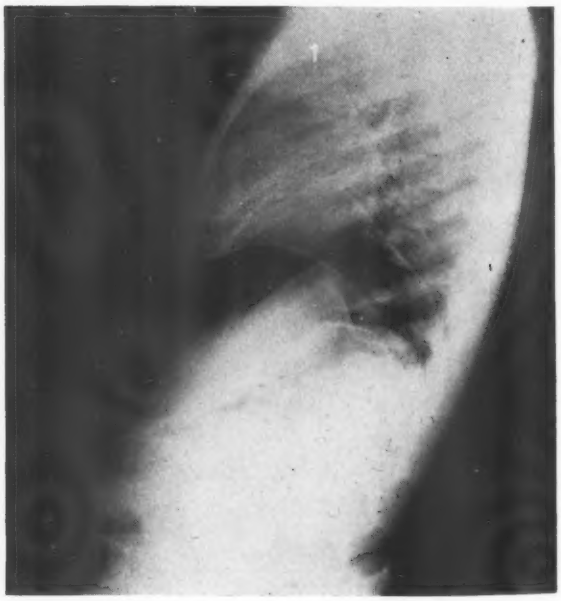


FIG. 6.—Lateral view after pneumoperitonium.

Films were then taken (Figs. 4, 5 and 6) and show decisively that the rounded shadow is due to an abnormality of the left leaf of the diaphragm, probably an area of diminished muscle tone. The boy's upper respiratory tract infection was dealt with, and contemplated further procedures, such as a bronchogram and aspiration, were abandoned.

Summary

A case is described on which the nature of a radiological opacity in the thorax was determined by diagnostic pneumoperitoneum.

I wish to thank Dr. Charles Pinckney and Mr. A. H. M. Siddons, under whose care the child was admitted, for permission to publish the case.

PAEDIATRIC SOCIETIES IN THE BRITISH ISLES

The following is a list of paediatric societies and their principal officers at the time of compilation. Alterations should be forwarded to the editors when they occur. Information on new societies or any omissions from this list should also be passed to the editors.

I: National

British Paediatric Association
President: Professor J. M. Smellie
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Llandough Hospital,
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The Children's Hospital,
Ladywood Road,
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South West Regional Paediatric Club
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Department of Child Health,
Children's Hospital,
St. Michael's Hill,
Bristol 2.

DUPLICATION OF THE ILEUM

BY

W. S. KILLPACK

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(RECEIVED FOR PUBLICATION JUNE 12, 1952)

Examples of cystic developmental abnormalities of the intestinal canal have been reported with increasing frequency during the past few years (Barrett, 1951; Aitken, 1950; Wooler, 1950; Webb, 1950).

Frequently these structures, which lie in intimate contact with the digestive tube, are the cause of an abdominal emergency with a characteristic clinical picture differing from that of an obstruction of the more normal type (Ladd and Gross, 1941). It is for this reason that anatomical descriptions are few and incomplete, as the associated strangulation with superadded infection obliterates the detail. The incidental discovery, therefore, during the necropsy of a newborn premature infant of an intestinal duplication has permitted the study of one of these developmental abnormalities in the intact state.

Necropsy Findings

A male infant weighing 4½ lb. was born six weeks prematurely and died two days later of atelectasis. An elongated cystic swelling was found on the mesenteric border of the ileum near the ileo-caecal valve. Unfortunately the mesentery was not kept intact, the bowel being removed from the body by cutting through the mesentery fairly close to the viscus, and therefore the actual arterial supply could not be investigated.

The cyst, which measured $6 \times 3 \cdot 2 \times 2 \cdot 5$ cm. before fixation, was tense, and lay between the two layers of the mesentery, with its distal extremity 5 cm. from the ileo-caecal valve (Fig. 1). The terminal mesenteric vessels could be seen coursing over its surface in a radial fashion (Fig. 2). The cyst contents were

FIG. 1.—Anterior view of cyst showing relation to ileo-caecal valve ×0·5.

FIG. 2.—Postero-inferior view of cyst showing terminal mesenteric vessels coursing over surface ×0·75.

FIG. 3.—Photomicrograph of cross section of cyst and ileum. Haematoxylin and eosin ×3·5.

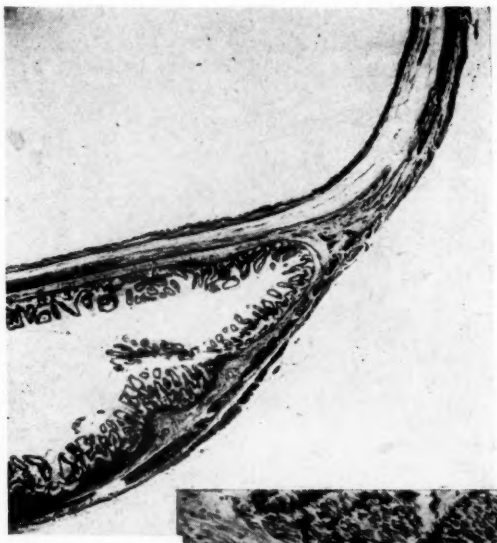

FIG. 4.—Photomicrograph of part of site of fusion of cyst with bowel. Iron haematoxylin and Van Gieson ×9·5

FIG. 5.—Higher power view than Fig. 4. The two types of epithelium are visible and the general arrangement of the muscular layers can be made out. Iron haematoxylin and Van Gieson ×80.

aspirated with difficulty through a wide-bore needle and replaced with 10% formol saline. The fluid was found to be glairy, clear and colourless, and contained a quantity of mucin. As the adjacent bowel contained meconium, the cyst could not be regarded as a diverticulum.

Some of the fluid was mixed with saline and centrifuged. The deposit consisted of a small number of ciliated columnar epithelial cells, round cells and amorphous debris. After thorough fixation the specimen was frozen and a slice, 0·5 cm. thick, cut for histological examination from the middle of both cyst and adjacent ileum. It was noted that the cyst lining was quite smooth to the naked eye and also that the lumen of the ileum, though apparently normal in size, was distorted in outline by the distended cyst to which it was intimately connected (Fig. 3).

Histological Examination. It was immediately apparent that cyst and bowel were separate structures though sharing a common longitudinal muscle coat (Fig. 4). Mucous membrane, muscularis mucosae, submucosa and circular muscle coats of the bowel were normal (Fig. 5). The cyst had a distinct mucosa composed of stratified polygonal, almost squamous, cells, the most superficial of which formed a continuous layer of ciliated epithelium (Fig. 6). There was a prominent muscularis mucosae, two or three times the thickness of that of the bowel, and a well developed independent circular muscle coat. As the cyst was considerably larger than the bowel the latter had the appearance of being a mere appendage of the former lying within its circular muscle coat; however, examination of numerous sections failed to show any definite continuity of fibres and the separate identity of the two circular muscle coats seems established. Secretion of mucin was not active, presumably due to pressure of contained secretion, and only an occasional goblet cell was demonstrable (Fig. 7).

Embryology

Double organs, usually imperfectly developed,

have their origin very early in embryonic life, and, particularly in connexion with tubular structures, are commonplace in surgery and pathology. The gross features in their development will not, therefore, be discussed here. However, a striking feature of the duplication cyst in this case was the continuous lining of ciliated epithelium. Normally the only part of the human digestive tube in which this type of epithelium is found is in the oesophagus and then only for a brief period in foetal life. Ciliated cells have been found at the 44 mm. stage, and they form a continuous layer by the eleventh week (65 mm. stage) to disappear slowly by desquamation towards the end of the sixth month (210 mm. stage). The histogenesis of the epithelial lining of the oesophagus has been summarized recently by Raeburn (1951) who describes the persistence of islands of ciliated epithelium in a woman of 35 years. Epithelium of the type lining this cyst is illustrated by Patten (1946) and appears to be normal for the 13-week-old foetus (85 mm. stage).

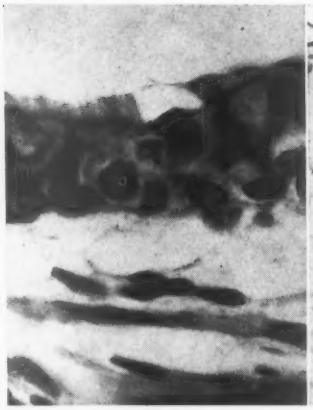

FIG. 6.

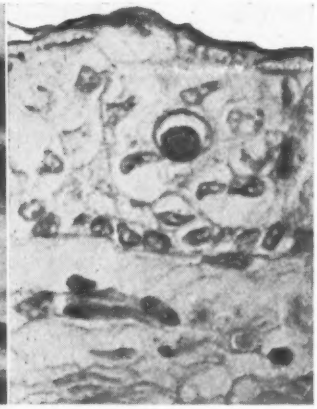

FIG. 7.

FIG. 6.—High power view of epithelium lining cyst showing cilia. Haematoxylin and eosin ×600.

FIG. 7.—High power view showing epithelial cell distended with mucin. Iron haematoxylin and Southgate's mucicarmine ×600.

There appears to be no reference in the literature to the certain occurrence of ciliated epithelium elsewhere in the normal digestive tube, though the early embryologists believed that the embryonic gastric mucosa was ciliated, on the basis of finding ciliated cells in the gastric contents. It seems certain, however, that these had been carried down from the oesophagus. Keibel and Mall (1910-12) found no evidence of gastric ciliation in their collection of embryos.

The heteropia described here is no less anomalous than the mucosa of gastric type commonly found in remains of the vitello-intestinal canal, or in the jejunal duplication described by Wooler (1950).

Discussion

The criteria laid down by Ladd and Gross (1941) for alimentary duplications may be summarized here as they are well exemplified in the present case: contiguity with, and firm adherence to, part of the digestive tube; a smooth muscle coat, usually of two layers; mucosal lining or epithelium similar to that of some part of the alimentary tract.

The salient features of the principal components of cyst and bowel may also be tabulated as follows:

	Cyst	Gut
Lining epithelium ..	Stratified, ciliated, of transitional type, mucus-secreting but doubtful goblet cells present	Normal
Muscularis mucosa ..	Well developed and prominent	Normal and prominent
Submucosa ..	Narrow, relatively acellular space	Normal cellularity
Muscularis Longitudinal .. Circular ..	Continuous over both. Prominent in both with fusion where gut and cyst are contiguous	
Serous coat ..	Terminal mesenteric vessels run here	Normal antemesenteric border

The majority of recorded instances of duplications have been blind cystic structures. Wooler's (1950) case, however, appears to have been a diverticulum, as there were two communications with the bowel. These however might have resulted from digestive ulceration.

The arrangement of the muscle coats and the blood supply in the instance described here clearly amplify the contention of Ladd and Gross (1941) that no attempt at removal by local dissection can be expected to meet with the smallest measure of success.

Summary

A further example of intestinal duplication is described in which there was the fullest opportunity for detailed investigation of its structure.

The findings are in accord with the descriptions in previously recorded cases and additional structural details are given.

I am indebted to Mr. C. J. B. Murray and Dr. W. Howard Hughes for helpful criticism.

Addendum

Since this paper was written Potter (1952) has described a further example of ileum duplex. The arrangement of the musculature is illustrated and is similar to that demonstrated here, except that the mucosal lining of the cystic portion is of small gut type. Potter encountered alimentary tract duplications only twice in over 9,000 foetal and neonatal necropsies.

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TWO CASES OF CHRONIC POLYNEURITIS IN CHILDREN

BY

J. S. OLDHAM

From the Children's Hospital, Birmingham

(RECEIVED FOR PUBLICATION JUNE 30, 1952)

Polyneuritis has been regarded as an uncommon disease in childhood. Formerly many cases have been due to diphtheria or lead poisoning but these conditions are now infrequent. In the past 25 years there have been numerous reports of the Guillain Barré syndrome, or acute infective polyneuritis affecting children. Hecht (1937) described seven personal cases and by 1941 Casamajor and Alpert had been able to find 38 recorded examples in children below the age of 12. Scheid (1946) reviewed the literature and concluded that this type of polyneuritis could not be regarded as rare during infancy and childhood.

Chronic and recurrent forms, however, appear to be very unusual. Thomson (1910) described a youth of 19 who developed an extensive flaccid paralysis a few days after he had fallen out of a sculling boat. The limbs, trunk and face were affected. Sensory symptoms were very slight. Recovery was slow but was complete after two years. At the age of 5 he had had a similar illness with recovery after 18 months.

Batten (1913) described recurring polyneuritis in a boy aged 8. The first episode lasted four months and chiefly involved the legs. Sensation was very slightly, if at all, affected. A second attack occurred four months later and the boy again made a good recovery. Batten also mentioned a girl aged 3 in whom the illness ran a relapsing course and ended fatally after 14 months. Details of a similar case have been given by Collier (1932). His patient was a girl aged 14 who died from bulbar paralysis five months after the onset of the illness.

Rabinowitz (1914) reported the case of a girl who had attacks at the ages of 9 and 12. On each occasion symptoms lasted some 12 months and there was considerable pain in the limbs. Nattrass (1921) published the case of a boy who had three attacks when aged 4, 17 and 18. There were sensory symptoms but no signs of impaired sensation. Where palpable, nerve trunks were abnormally thick and hard. Brain (1933) mentions a boy aged 15 seen in his fourth attack, the first having occurred at the age of 4.

Case Reports

Case 1. A girl aged 13, the youngest child in a family of five, was admitted to the Royal Salop Infirmary in December, 1949. For one month she had noticed gradually increasing weakness of the arms and legs. She had experienced no pain and there had been no preceding febrile episode.

Examination revealed a symmetrical flaccid paralysis of the limbs, most pronounced peripherally. Tendon reflexes in the legs were absent and those in the arms much reduced. The superficial abdominal reflexes were present. There was slight muscle wasting but no tenderness. No impairment of any form of sensation could be demonstrated.

The cerebrospinal fluid contained 60 mg. protein per 100 ml. with a slight excess of globulin (Pandy test). A cell count gave 1 lymphocyte per c.mm. The blood count and sedimentation rate were normal, with no basophil stippling of the red blood cells. The urine was normal; no lead or porphyrins were detected. The Schick Test was negative. *C. diphtheriae* was not isolated from nasal and throat swabs.

The paralysis increased and spread to involve the trunk and the muscles of the neck, face and tongue. All tendon jerks were lost. Within two months of her admission to hospital she was completely helpless. No movement was possible in the limbs nor could she raise her head from the pillow. Muscle wasting became extreme, and the muscles showed loss of contraction to faradic current and gave only a very feeble response to galvanism.

There was great weakness of the facial muscles and masseters; the tongue was grossly wasted and showed pronounced fibrillation. As the illness progressed dysphagia became increasingly severe, phonation became very weak and she had difficulty in coughing and in clearing her throat of secretions. Eventually tube feeding had to be employed, and suction used to prevent

distressing choking attacks. Finally respiratory embarrassment from involvement of both intercostal muscles and the diaphragm became so great that a respirator was necessary for two weeks. Tachycardia developed, the highest pulse rate recorded being 180/min. An electrocardiogram at this time showed sinus rhythm and no abnormality of the complexes.

During the past two and a half years there have been periods of improvement and of relapse, but the patient remains severely paralysed. At no time has there been any pain, sphincter disturbance, or impairment of sensation. In treatment antibiotics, aneurine, and prostigmin have been employed without benefit.

This patient previously had an illness of identical pattern when aged 9. The onset was slow but within three months there was complete paralysis of the limbs, and the trunk, facial muscles, masseters and tongue were involved. However she did not on that occasion experience dysphagia or choking attacks. There were no sensory symptoms nor signs of sensory loss. Improvement began after a year, and she was able to walk some 18 months after symptoms had first been noticed. She eventually returned to school, played games, and rode a bicycle. Recovery had appeared complete before her second attack began in November, 1949.

Case 2. A girl aged 8, an only child, was well until February, 1951, when she was noticed to be using both hands when turning door knobs, and to have difficulty in buttoning her clothes and in tying her shoelaces. A week later she began to walk clumsily and became unable to mount stairs. She had no pain and there was no history of any recent illness. She was admitted to the Birmingham Children's Hospital on April 26, two months after symptoms had first been observed. There was found to be symmetrical weakness of all the limbs most pronounced at the periphery, with moderate muscle wasting. The muscles were not tender. Power in the trunk muscles was normal. All tendon reflexes were absent but the superficial abdominal reflexes were present. No definite defect of any form of sensation could be demonstrated. The cranial nerves were normal.

The blood count was normal, with no basophil stippling of red blood cells. The sedimentation rate estimated by a micro method was 3 mm. in one hour. In the cerebrospinal fluid there was 1 lymphocyte per c.mm. and 80 mg. protein per 100 ml. Throat and nose swabs were negative for *C. diphtheriae*. The Schick Test was negative. There were no lead or porphyrins in the urine. Radiographs of the long bones showed no evidence of lead deposition. The blood pyruvate level was 1 mg./100 ml. An electrocardiogram was normal.

She was treated with aneurine and given light massage and passive movements. She improved slightly and the cerebrospinal fluid on May 8, 1951, contained less protein (50 mg. per 100 ml.). She was allowed to go home on June 16, but three weeks later was re-admitted as her condition had considerably worsened. All power in the hands and feet was now lost and there was complete bilateral wrist and foot drop. A little power remained in the shoulders and hips. Some weakness of the trunk musculature had developed. There was considerable muscle wasting in the limbs. Electrical stimulation of the affected muscles gave a normal reaction to galvanism but only a weak response to faradism. Sphincter control remained normal. The C.S.F. was examined again on September 6, when the protein content had risen to 120 mg. per 100 ml. Improvement was slow but 14 months from the beginning of her illness she could use a spoon and fork, raise her arms above her head to brush her hair, and was beginning to walk with the aid of leg supports.

Discussion

In neither of these cases could the cause of the illness be found. In both a purely motor type of polyneuritis developed gradually and ran a prolonged course. There was no history of any preceding febrile disturbance, and no sensory symptoms. The cerebrospinal fluid contained an excess of protein, the cell count remaining normal. The protein increase was more pronounced in Case 2, rising to 120 mg. per 100 ml., and this case might be regarded as an instance of the Guillain Barré syndrome, or acute infective polyneuritis. Against this view are the absence of sensory symptoms, the pronounced muscle wasting and the long duration of the illness. The two cases resemble each other closely. They differ only in the severity and extent of the paralysis and seem to be examples of the same condition. The clinical features suggest that the cause may have been some slowly acting toxin rather than an infection.

Recurrence after two years took place in Case 1. Most examples of recurrent polyneuritis of unknown cause have occurred during adult life and the symptomatology has been very varied. The literature has been reviewed by Ungley (1933) and by Stucke (1947). Ford (1944) considers that this is a heterogeneous group of conditions and that no single explanation can be applied to all cases.

Collier (1932) referred to several cases in which second or third attacks of peripheral neuritis had occurred after intervals of months or years, and no causal agent had been found. In each the organism of diphtheria was eventually recovered from one or other of the paranasal sinuses, and he considered that diphtherial infection of the chronic carrier order was the most common cause of recurring neuritis. In neither of the present cases was the Klebs-Loeffler bacillus found. There was no accommodation palsy, and both the long duration and the severity of the paralysis appear to exclude a diphtheritic origin.

Harris (1922) described a case which is strikingly similar to Case 1. His patient, a girl of 15,

developed an extensive flaccid paralysis with involvement of the face and tongue. There was no sensory loss and the only sensory symptoms were slight paraesthesiae of the finger tips early in the illness. Recovery did not begin for 18 months but was complete two years later. She was well at the age of 31 and had not experienced any recurrence. Harris (1935) referred again to this case in a paper in which he reviewed the chronic forms of polyneuritis. He considered that there was a group showing common features of slowly progressive motor paralysis with muscle wasting, changes in the electrical reaction of the muscles, and few sensory changes. Both recurrence after a short period of complete recovery and neural hypertrophy were features which might or might not be present. He suggested that the cause might be an endotoxin, and that such cases might be classed under the term chronic progressive (endotoxic) polyneuritis.

The prognosis of polyneuritis in childhood is considered to be good. Death is rare and when it has occurred has generally done so early in the course of the disease as a result of a rapidly spreading paralysis of the Landry type. It is usual for recovery to be rapid and complete, but the two cases I have reported are a reminder that chronic and recurrent forms may occur in children.

Summary

Two cases of chronic polyneuritis are described. The cause was not determined. In one recurrence took place after two years.

The literature is reviewed.

My thanks are due to Dr. C. L. Stote and to Dr. C. G. Parsons for permission to publish details of their cases.

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BOOK REVIEWS

Poliomyelitis. By W. RITCHIE RUSSELL. (Pp. 81. 14*s.*) London: Edward Arnold. 1952.

In this small book Dr. Ritchie Russell makes a valiant attempt to outline concisely the present state of our knowledge of the many aspects of poliomyelitis. Based on his wide experience, he puts together a lucid and practical account both of what we know and of the problems which remain to be solved in the future.

There are few aspects of poliomyelitis on which the author does not touch and not unnaturally the management of the disease receives the greatest emphasis. In presenting the evidence for and against closing a school where there is an outbreak of poliomyelitis, or again in considering the problem of tonsillectomy during poliomyelitis epidemics, the author is almost too commendably objective and one would have liked to hear his personal views stated rather more categorically.

The book can be recommended with confidence to all those who are concerned not only with the management of established cases, but also to the general practitioner on whose shoulders usually falls the onus of having to suspect the possibility of poliomyelitis. Lastly, it will not be without interest to those concerned with the later stages of the disease and rehabilitation.

Food and Nutrition. 2nd edition. By E. W. H. Cruickshank. (Pp. 443. 30*s.* net.) Edinburgh: E. & S. Livingstone. 1951.

Eating is a subject on which we are all expert because we have years of experience of it, a bundle of prejudices, racial, familial and personal, and a sketchy memory of the physiology we once studied.

Most of us seem so ignorant about dietetics that one is tempted to recommend this as a standard book which all medical students should spend a term studying. A house physician will request the dietitian to send up a 'low-protein diet' for a child getting over acute nephritis, instead of asking the ward sister to 'see that Jimmy has half a pint of milk, and one egg a day, no meat or fish', etc.

This book is a good one; I hope that all qualifying doctors will read it during their pre-registration year. There is a good historical survey, especially of the last quarter century in Britain, with a glance at the world's problems, and the chapters on bread, milk and edible oils are very good reading. If margarine is flavoured to taste like butter, most animals will eat much greater amounts, but humans are more successfully tempted by colouring it and serving it in pats. Hospital organizers will find the book helpful on dietary planning.

Chapter XX on the appraisal of the nutritional state in individuals (and communities) is an important one, and as this is the problem on which the clinician will be asking help it should be very clearly set out. It is too dogmatic to say 'a well nourished person will stand erect' (page 409), and 'the wilful child who refuses to drink milk . . . can be disciplined to . . . alacrity in eating, if parents will but take the trouble, and it may be considerable trouble, to maintain a dietary discipline'. Posture is a complex affair, but there are many adolescent girls who droop, because they are self-conscious about their recently acquired tallness and breasts; they are well fed but they will not stand erect. The second quotation may be true, but the end of the struggle may be alacrity in obeying the parental order to drink the milk and an equally quick vomit or a lasting distaste for it. Are the Chinese so much worse off for not placing so much emphasis on milk for children? Can they not have eggs and cheese, etc.? The meal table is an unsuitable place for teaching dietary discipline; it is the place to teach children to enjoy food, eating and meal times.

One is glad to see (p. 410) emphasis on the need for rest if children are to grow well, and sorry that after we have read on p. 318 that a cheese roll is a much better *meal* than roast mutton with two vegetables and a sweet; on p. 421 we are told that a school meal should be served hot.

The 'Oslo breakfast' is scandalously neglected. Introduced with care into factories and schools during the last war, it became very popular. One would also like to have seen reference to Widdowson's 1947 'Study of Individual Children's Diet' (M.R.C. Special Report No. 257). We can all make suggestions; Professor Cruikshank has made a fine book.

The Convalescent Child. By FRANK FALKNER. (Pp. 49, plus 6 pages of references and 3 diagrams.) Liverpool: Wilmer Bros., University Press. 1952.

This is less a study of the convalescent child than of convalescence in childhood, and as such it fulfils a useful purpose in bringing into the light a neglected subject.

The writer notes the haphazard nature of the arrangements for convalescence in this country, the unevenness with which homes are distributed geographically, and the lack of suitable homes for certain types of children, such as adolescent boys. He points out such anomalies as the requirement that teachers in long-stay homes shall conform to standard hours of work and holidays. He is a strong advocate of convalescence at home, but lack of space has not allowed him to discuss fully the difficulties in the way and how to overcome them.

This is a useful booklet for any student of child health, and a certain scrappiness may serve to stimulate the production of a more comprehensive and detailed review of an important part of the care of the sick child.

Die Zerebrale Angiographie. By H. KRAYENBÜTH and H. R. RICHTER. (Pp. VIII+213; 100 illustrations. D.M. 597.) Stuttgart: Georg Thieme. 1952.

One has no hesitation in commending this book to all interested in the central nervous system. It is fully illustrated with excellent reproductions of cerebral arteriograms, nearly all accompanied by line drawings with the principal vessels identified and the abnormalities clearly indicated.

A quick perusal of the illustrations would soon convince one of the value of cerebral angiography as a diagnostic procedure. In the years that have passed since Moniz performed the first carotid arteriogram (1927) many of the possibilities of the examination have been realized, as this volume shows. In particular much of the authors' recent work on the normal and pathological anatomy of the deep cerebral veins is included. It used to be believed that cerebral angiography was of no value in the localization of central tumours when pathological vessels were not demonstrable. However, now that the radiological anatomy of the deep veins has been described, it is possible to localize these tumours by the manner in which they dislocate veins even when the cerebral arteriogram is substantially normal. It is not reasonable, however, to expect more accuracy than is obtained by pneumography.

As a neuroradiologist I would like to have seen more of the lateral arteriograms accompanied by antero-posterior projections, but this could only have been done at the cost of reducing the number of cases reported.

The bibliography is comprehensive.

Residential Speech Therapy. Edited by C. WORSTER-DROUGHT. (Pp. 150; illustrated. 15*s*.) London: Wm. Heinemann Medical Books Ltd. 1952.

Some children with defective speech, due to a variety of causes, need more observation and treatment than can be provided in one or two weekly attendances at an out-patient clinic. Moor House School was opened in 1947 for such patients, and this book is an account of its first two years' work and of the first 36 children who were accepted as residents. It is often difficult for outsiders to know what goes on in new and specialized institutions, hence the value of this account. It is truly original, for it describes what was observed without attempting any detailed survey of the work of others in the field of speech therapy, and those who have to deal with serious cases of this type will find the book interesting and useful. The literary style is clear, technical and unadorned: there are illustrations, tables, appendices and an index.

Corrections

The Editors regret that in the title of the paper by A. M. G. Campbell, Joan Guy and W. Grey Walter published in the December, 1952, issue of the *Archives of Disease in Childhood* (**27**, 507), the word "cytomegalic" was inserted. The correct title should be "Two Cases of Inclusion Encephalitis".

In the paper "Vomiting of Uncertain Origin in Young Infants," *Archives of Disease in Childhood*, **27**, 562, the legend to Fig. 1 should read: "Comparison of average growth curves in persistent and non-persistent vomiting of uncertain origin."

The vertical lines (Max.) indicate the maximum deviation from the normal weight, which occurs at very different ages in the two groups.

The first four words of line 15, column 2, page 563 should be deleted.